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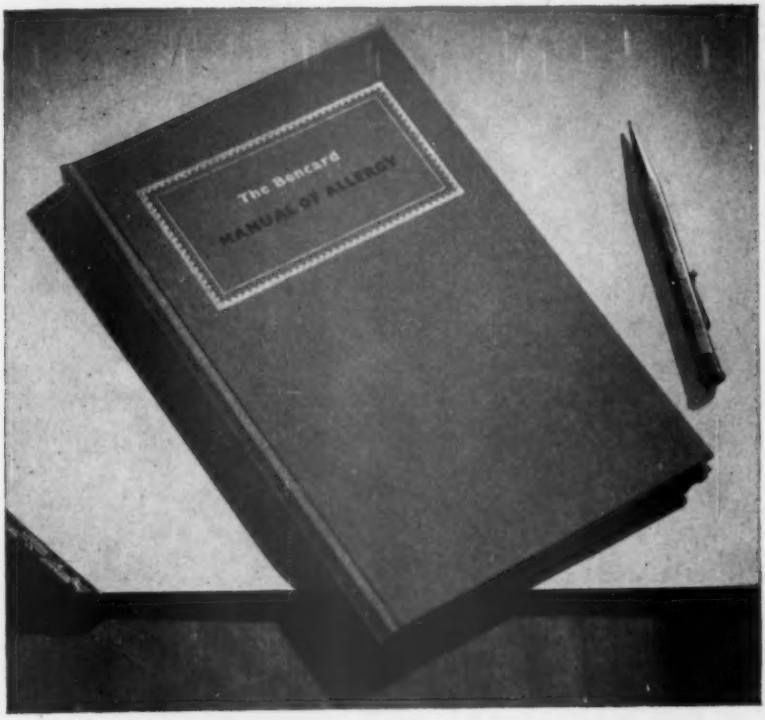

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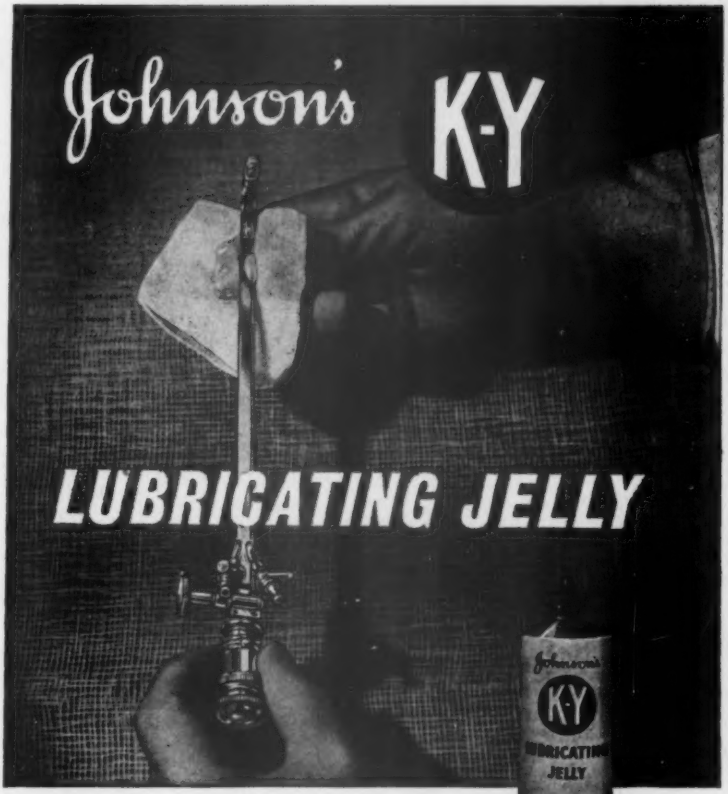

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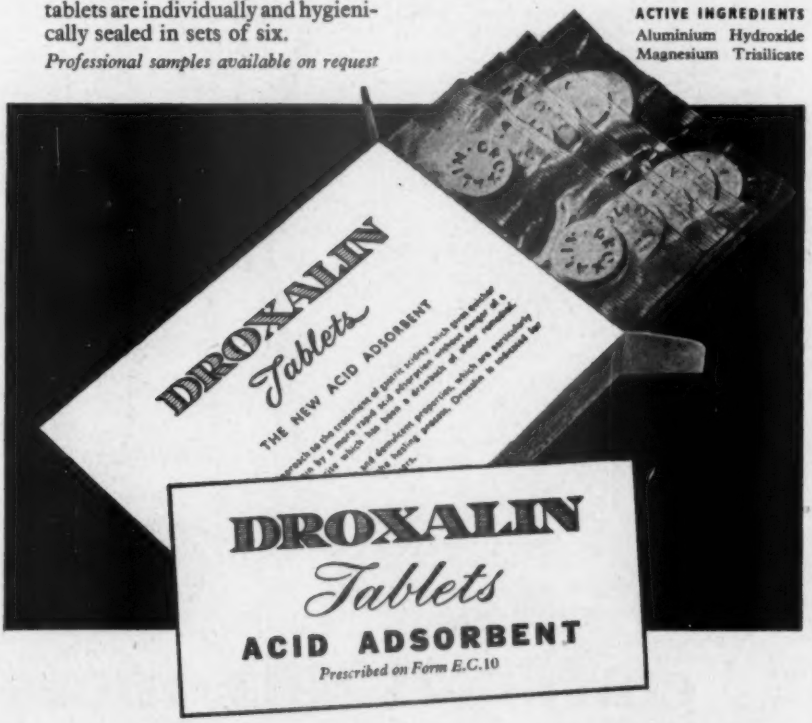

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The flowers that bloom in the Spring, tra la

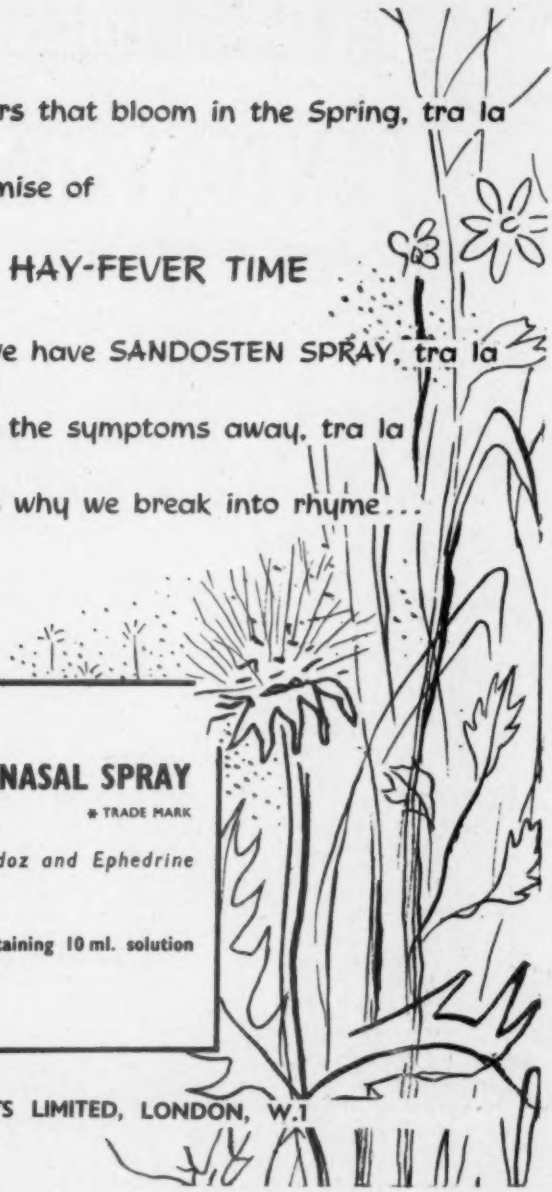
Breathe promise of

HAY-FEVER TIME

But now we have SANDOSTEN SPRAY, tra la

To chase all the symptoms away, tra la

And that's why we break into rhyme...



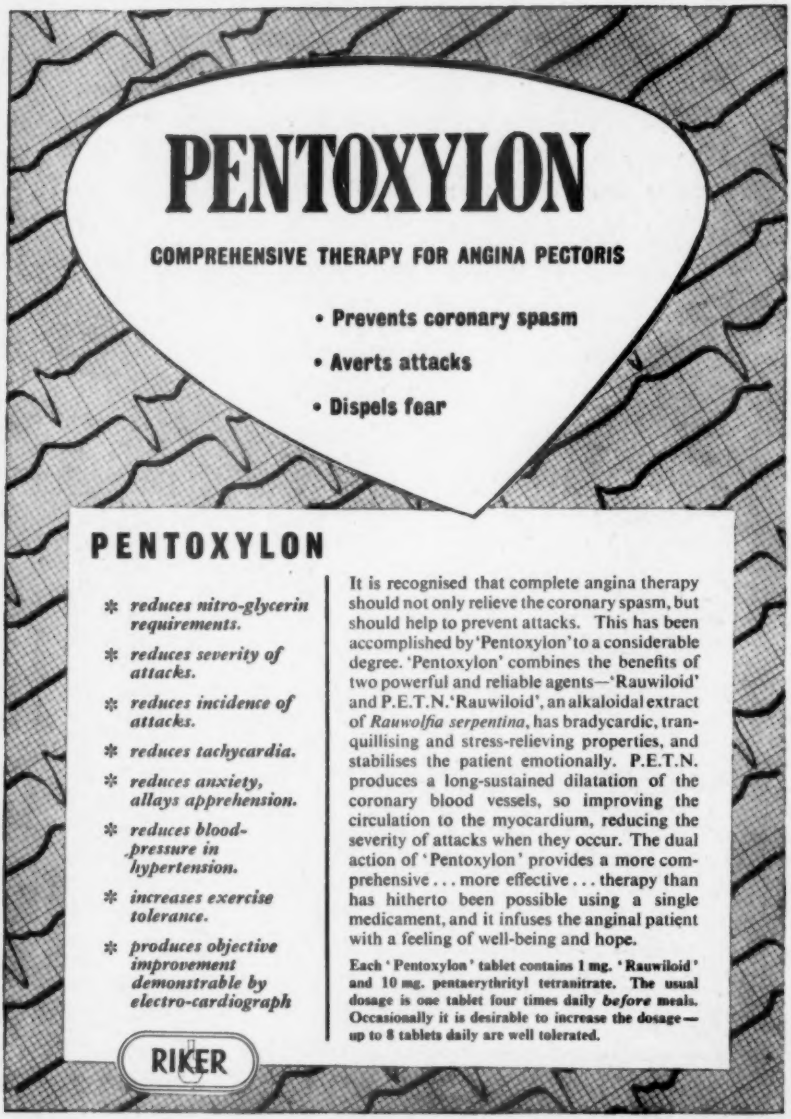
SANDOSTEN* NASAL SPRAY

(thenalidine) * TRADE MARK

with Calcium-Sandoz and Ephedrine

Plastic nebulizers containing 10 ml. solution

SANDOZ PRODUCTS LIMITED, LONDON, W.1



PENTOXYLON

- ✲ *reduces nitro-glycerin requirements.*
- ✲ *reduces severity of attacks.*
- ✲ *reduces incidence of attacks.*
- ✲ *reduces tachycardia.*
- ✲ *reduces anxiety, allays apprehension.*
- ✲ *reduces blood-pressure in hypertension.*
- ✲ *increases exercise tolerance.*
- ✲ *produces objective improvement demonstrable by electro-cardiograph*

It is recognised that complete angina therapy should not only relieve the coronary spasm, but should help to prevent attacks. This has been accomplished by 'Pentoxylon' to a considerable degree. 'Pentoxylon' combines the benefits of two powerful and reliable agents—'Rauwiloid' and P.E.T.N. 'Rauwiloid', an alkaloidal extract of *Rauwolfia serpentina*, has bradycardic, tranquillising and stress-relieving properties, and stabilises the patient emotionally. P.E.T.N. produces a long-sustained dilatation of the coronary blood vessels, so improving the circulation to the myocardium, reducing the severity of attacks when they occur. The dual action of 'Pentoxylon' provides a more comprehensive . . . more effective . . . therapy than has hitherto been possible using a single medicament, and it infuses the anginal patient with a feeling of well-being and hope.

Each 'Pentoxylon' tablet contains 1 mg. 'Rauwiloid' and 10 mg. pentaerythrityl tetranitrate. The usual dosage is one tablet four times daily *before* meals. Occasionally it is desirable to increase the dosage—up to 8 tablets daily are well tolerated.

RIKER

'Pentoxylon' is a regd. trademark. Regd. users: RIKER LABORATORIES LIMITED LOUGHBOROUGH, LEICS.

'Hydrocortistab'

TOPICAL HYDROCORTISONE PREPARATIONS

A comprehensive range to meet every requirement in dermatological and ophthalmological practice

Skin ointment
Eye ointment
Eye drops
Cream
Lotion

'Hydromycin'

HYDROCORTISONE AND NEOMYCIN

Skin ointment
Ear/Eye ointment
Ear/Eye drops

Full details of strengths and sizes gladly sent on request

BOOTS PURE DRUG COMPANY LTD. NOTTINGHAM ENGLAND

Swann-Morton

SURGICAL BLADES AND HANDLES

TRADITIONAL AND INTERNATIONAL

These eleven shapes of surgical blade have become traditional and—international. Hospitals all over the world send to Sheffield for ever increasing supplies; so the model factory built to produce Swann-Morton blades is always expanding. But, however great the pressure of orders, there is never any relaxation of the individual care given to each individual blade.

FIVE SIZES OF HANDLES, PRECISION MADE, COMPLETE THE RANGE

W. R. SWANN & CO. LTD., SHEFFIELD, 6. ENGLAND

1786C

with

V

ACHROMYCIN* V

TETRACYCLINE BUFFERED WITH SODIUM METAPHOSPHATE

Absorption is faster . . . blood levels higher

ACHROMYCIN V is Lederle's latest contribution to medical science. It results from research on methods of increasing the therapeutic potency of ACHROMYCIN tetracycline—already recognised as today's foremost self-sufficient broad-spectrum antibiotic. ACHROMYCIN V consists of ACHROMYCIN tetracycline buffered with sodium metaphosphate—believed to have the ability of binding certain metal ions present in the intestinal tract, which when free, combine with some of the tetracycline and prevent its absorption. ACHROMYCIN V possesses the following advantages:—

It is more rapidly absorbed from the intestinal tract
It provides higher blood levels of tetracycline more quickly
The higher blood levels are longer lasting

SUGGESTED DOSAGE: As for ACHROMYCIN i.e. for the average adult 1 Gm. DAILY in divided doses.

ACHROMYCIN V is presented in oral capsules containing 250 mg. ACHROMYCIN tetracycline, and 380 mg. Sodium Metaphosphate.

Bottles of 16, 100 and 1,000 Capsules

* Regd. Trademark

Lederle

LEDERLE LABORATORIES DIVISION
CYANAMID OF GREAT BRITAIN LTD., LONDON, W.C.2

QUADRIN

TRADE MARK

NON-HORMONAL TREATMENT FOR TH

FORMULA

Ammonium chloride	0.3 g.
Reserpine	0.2mg.
Homatropine methylbromide	0.5mg.
Caffeine	0.03 g.

Presented in bottles of 50 sugar-coated tablets.

Available under N.H.S. prescription.

WARD. CAS

THE PREMENSTRUAL SYNDROME

REDUCES—

Sodium and water retention, source of central and autonomic nervous disorders.

COMBATS—

The central and autonomic nervous symptoms and the tendency to hypertension.

RELIEVES—

The spasmodic pains in the pelvis, abdomen and breasts.

CASSENNE LTD., 116, VICTORIA STREET, LONDON S.W.1.

Tomorrow she will be in hospital undergoing an operation. Not a serious one, and she's not looking very serious about it, is she? She's a sensible girl and has complete faith in modern medicine and surgery. The doctors and nurses who look after her in hospital put *their* trust in British Oxygen equipment and gases. Like hers, their trust is well founded.

BOC **BRITISH OXYGEN**

BRITISH OXYGEN GASES LTD., MEDICAL DIVISION GREAT WEST ROAD BRENTFORD, MIDDLESEX

Makers and suppliers of anaesthetic, analgesic and therapeutic equipment and gases

When fluid contents exceed requirements

DIAMOX*

*REGD TRADE MARK

ACETAZOLAMIDE

Lederle

In conditions where excess fluid accumulates in body tissues, prompt, dispersal measures are called for. In such cases, by inhibiting carbonic anhydrase, DIAMOX acetazolamide produces prompt copious diuresis. It has proved its ability to control body-fluid balance in cardiac oedema, glaucoma and epilepsy. Published reports also show satisfactory results from DIAMOX in toxaemia and oedema of pregnancy, premenstrual tension, renal oedema, emphysema and drug-induced oedema. DIAMOX is a welcome departure from the mercurials and is well suited to long-term maintenance of ambulant and out-patient cases.

TABLETS of 250 mg.

BOTTLES of 25, 100 and 1,000

PARENTERAL Vials of 500 mg.

LEDERLE LABORATORIES DIVISION

Cyanamid OF GREAT BRITAIN LTD. London W.C.1

it's no picnic having hay-fever. . .

. . . but here's a simple remedy

Whether it's a picnic or polo, punting or putting, the allergic patient's summer activities need not be marred. Ef-Cortelan Nasal Spray will gently suppress the symptoms of hay-fever, vasomotor rhinitis and other common inflammatory allergic conditions of the nose. Pleasant, inexpensive, it is simply administered by means of it's own plastic squeeze bottle.

EF-CORTELAN TRADE MARK NASAL SPRAY

Hydrocortisone alcohol 0.02% Naphazoline nitrate 0.025% In 15 cc. spray bottle.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX. BYRon 3434

Makers of ALL that's needed for corticosteroid treatment

Zicthol and Pixcyl

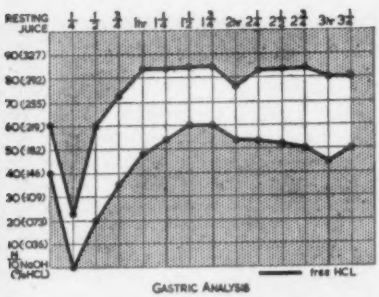
For each stage of Eczema-Dermatitis an appropriate treatment

In whatever phase Eczema-Dermatitis may present itself, there is a product in the Genatosan dermatological range to afford early relief and effective medication.

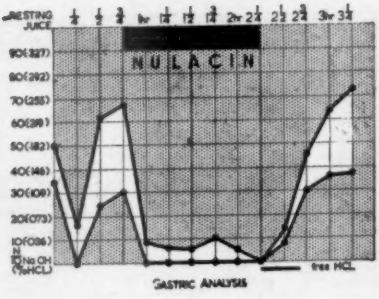
ACUDEX for the acute stage, **ZICTHOL** for the sub-acute and for infantile eczema, **ZICTHOL GREEN** for the secondary infected and **PIXCYL** for the chronic. Between them they provide the appropriate treatment for any of the numerous manifestations of the Eczema-Dermatitis group of lesions.

Available on E.C.10.

Genatosan Limited, Loughborough, Leicestershire



GASTRIC ANALYSIS



GASTRIC ANALYSIS

In the treatment of peptic ulcer— safe, simple, effective, without side effects

NULACIN

provides milk-alkali drip therapy

The most effective control of gastric acidity is by milk-alkali drip therapy; the most convenient way of obtaining milk-alkali drip therapy is by sucking Nulacin tablets.

peptic ulcer in the ambulatory patient

Nulacin is of great value in the treatment of peptic ulcer in the ambulatory patient, and in the prevention of ulcer relapse.

clinical trials in three continents

Extensive clinical work has confirmed the claims made for Nulacin. References to some studies appear below. Other references will be given on request.

Nulacin tablets are not advertised to the public, have no B.P. equivalent and may be prescribed on E.C.10. The dispensing pack of 25 tablets is free of purchase tax. Basic price to N.H.S. is 2/-. Also available in tubes of 12.

Nulacin is available throughout the British Commonwealth, in the U.S.A., and in many other countries. It is known as Nulactin in Canada and Sweden.

SELECTED REFERENCES

Antacids, *The Practitioner*, January, 1957, **178**: 43

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Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer, *Amer. J. Dig. Dis.*, March, 1955, **22**: 67-71

Further Studies on the Reduction of Gastric Acidity, *Brit. Med. J.*, 23rd January, 1954, **1**: 183-184

Clinical Investigation into the Action of Antacids, *The Practitioner*, July, 1954, **173**: 46

The Control of Gastric Acidity, *Brit. Med. J.*, 26th July, 1952, **2**: 180-182

HORLICKS LIMITED

Pharmaceutical Division

SLOUGH, BUCKS

*

DIPASIC

Tablets of 100 mg. of isonicotinic acid hydrazide-p-aminosalicylate

The oral chemotherapeutic for TUBERCULOSIS

"The most striking change following treatment with Sa (Dipasic) is the remarkable lowering of the positivity of the sputum in a group of patients suffering from chronic bilateral pulmonary tuberculosis with cavitation."

Reprint from "British Medical Journal," October 22nd, 1955.

DIPASIC IS AVAILABLE FOR INVESTIGATION

GEIGY

* *DIPASIC is a chemical compound formed by the combination of INH and PAS in molecular proportions*

Literature available on request

BENGUE & COMPANY LTD. *Manufacturing Chemists*

MOUNT PLEASANT ▸ ALPERTON ▸ WEMBLEY ▸ MIDDLESEX

Bengue & Co. Ltd. make "Dipasic" available in the United Kingdom by arrangement with Ed. Geistlich Sons Ltd., Wolhusen (Switzerland)

in the chronic worrier

DRINAMYL

produces a mood of calm composure

Anxiety, apprehension or depression may cause or complicate a multitude of ills. An encouraging smile or a verbal pat on the back may help some patients to dismiss a baseless worry. But the chronic worrier needs more than encouragement if the troubles that shadow her life are to be met resolutely. 'Drinamyl' produces the peace of mind that such patients so desperately need. Smoothly and unobtrusively emotional tension is eased: harassment and anxiety give place to calm composure. The patient's competence to cope with problems is restored, and the response to treatment improved.

Drinamyl for the harassed patient

'DRINAMYL' TABLETS · 'DRINAMYL SPANSULE' SUSTAINED RELEASE CAPSULES

Smith Kline & French Laboratories Ltd.
Coldharbour Lane, London SE5

DLP86

But there are other ways—

in dealing with seborrhoea capitis

Simple seborrhoea can be brought under control by the weekly use of Genisol, applied in the manner of a shampoo. Genisol has been formulated to remove the loose scales, at the same time stimulating the production of normal tissue: the inclusion of hexachlorophene prevents aggravation of the condition by bacterial invasion.

Persistent seborrhoea capitis quickly responds to the combined treatment of Genisol-Sebigen. Sebigen should be rubbed into the scalp twice daily through numerous partings in the hair, followed by frequent applications of Genisol as directed.

Genisol and Sebigen *Prescribable on E.C.10*

Genatosan Limited, Loughborough, Leicestershire.

DETERGENTS AND THE SKIN

"We have found ... that the incidence of skin trouble attributable to synthetic detergents is no higher than that previously due to the use of soap products, alkalis and allied preparations"

REPORT OF THE GOVERNMENT COMMITTEE ON SYNTHETIC DETERGENTS, 1956

The vital role of detergents to-day

SINCE THEIR introduction six years ago the new washing products, now generally known as "detergents," have revolutionised British household washing. This is because they give superior performance in hard water, leave clothes and dishes demonstrably cleaner, and leave no dulling film as soaps usually do.

Women have been quick to appreciate these advantages. Thus, while the first weekly wash detergent (Tide) only achieved national distribution in September 1952, detergents as a whole now account for more than half of the total washing powder market. They are in constant and regular use in practically every home in this country, and there is no evidence that they have yet reached the peak of their popularity.

THEIR EFFECT ON THE SKIN

Thomas Hedley & Co. Limited, makers of Tide and other detergents, constantly test their washing products to determine their effect on the skin of housewives. In addition to every kind of accepted laboratory technique, such as patch and immersion tests, Hedley have conducted, under careful medical supervision, prolonged home usage tests. These were developed to obtain a reliable measure of the mildness of washing products under normal usage conditions in the home.

Observations on over 12,000 housewives have shown that household detergents as a class do not differ in their effect on the skin from all-purpose soap powders, as a group, which have been used for years.

Specifically, research has shown that Tide, the most popular of the new detergents, is as mild as other conventional general-purpose soap powders.

Moreover, the results of the Hedley investigations disclosed that a washing product plays a much smaller part in determining the skin condition of the average housewife than does, for example, the coldness of the weather and the extent to which she uses hand cream.

The conclusions from these tests are fully in line with the Report of the Government Committee on Synthetic Detergents, 1956, which stated "We **have found . . . that the incidence of skin trouble attributable to synthetic detergents is no higher than that previously due to the use of soap products, alkalis and allied preparations.**"

"A STUDY OF THE EFFECT OF THE NEW DETERGENTS ON THE SKIN"

This is the title of a booklet which describes a comprehensive research programme carried out under medical supervision to determine the effect of detergents on the skin. If you would like a copy, please send your request on a post card with your name and address, to Thomas Hedley & Co. Limited, Dept P., Gosforth, Newcastle upon Tyne 3.

TAMPAX encourages women to lead a normal life during the monthly period. The special Tampax applicator, an integral part of tamponage, ensures correct placement in the upper end of the vaginal tract and prevents any handling of the tampon. The comfort and security afforded by Tampax helps to eliminate the "invalid" complex.

Professional samples and literature will gladly be supplied by Medical Dept., Tampax Ltd., Belvue Road, Northolt, Greenford, Middlesex.

SANITARY PROTECTION WORN INTERNALLY

FIRST oral trichomonacide

TRITHEON*

BRAND OF AMINITROZOLE **TABLETS** TRADE MARK

for male and female.

Because of their systemic action, TRITHEON tablets reach resistant trichomonads throughout the genito-urinary tract.
Unlike local trichomonacides, TRITHEON tablets eradicate the organism in male and female as proved by *negative culture.*

To assure maximum effectiveness, simultaneous treatment of both husband and wife with oral TRITHEON tablets is recommended.

For rapid relief of vaginal irritation and to combat associated bacterial infection TRIPLE SULFA CREAM may be prescribed as adjunctive therapy in the female.

Dosage: One tablet three times daily for 10 days, repeated in resistant cases.

Available: Bottles of 30, 100 and 1000 tablets; each tablet contains 100mg 2-acetylamino-5-nitrothiazole.

LITERATURE ON REQUEST

Ortho

Ortho Pharmaceutical Limited • High Wycombe • England

* TRITHEON is the original brand of 2-acetylamino-5-nitrothiazole tablets developed in the Ortho Research Foundation for the oral treatment of trichomoniasis

when the clinical problem is a "common" infection

OF TISSUE, TRACT OR SYSTEM

*Albamycin**

BECAUSE: Blood concentrations with orally-effective Albamycin are 10 to 50 times higher than with other antibiotics, and significant serum concentrations persist 24 hours or longer; a broad therapeutic range is provided by bactericidal activity against Gram-positive and a certain few important Gram-negative pathogens (including susceptible strains of staphylococci and Proteus resistant to other antibiotics); clinical response is prompt in the majority of common infections; gastro-intestinal tolerance is excellent; cross-resistance with other commonly used antibiotics is unknown.

Adults: 500 mg. every 12 hours. ***Children:*** 15 mg/Kg. of body weight per day, in divided doses every 6 or 12 hours. ***Supplied:*** Albamycin Tablets, 250 mg., bottles of 16 and 100. Albamycin Syrup (125 mg. per 5 cc. teaspoonful), bottles of 2 fluid ounces.

*TRADEMARK FOR UPJOHN'S BRAND OF NOVOBIOCIN

Upjohn *Fine pharmaceuticals since 1886*

UPJOHN OF ENGLAND LTD • CRAWLEY • SUSSEX

asthma
preventative

ORTHOXINE®

Particularly suited to continued use for those patients most susceptible in certain seasons

Minimal pressor effects

With only 1/8 the pressor effects of ephedrine, the benefits of Orthoxine may be extended to asthmatic patients with concomitant hypertension or cardiovascular disease.

Negligible CNS effects

The nervous system excitatory effects of Orthoxine are minimal. Orthoxine lets the patient sleep. Daytime relief is obtained without nervousness or "over-alert" feeling.

More air for the majority

Orthoxine is especially effective in mild to moderately severe asthma. It eases burdened respiration and has been reported to increase vital capacity by as much as 1.1 litres of air.

Dosage: Adults — ½ to 1 tablet every 3 to 4 hours as required.
Children — ¼ to ½ tablet every 3 to 4 hours as required.
Supplied: 100 mg. tablets in bottles of 25 and 100.

® REGISTERED TRADEMARK

Upjohn

Fine pharmaceuticals since 1886

UPJOHN OF ENGLAND LTD · CRAWLEY · SUSSEX

Relief...

The relief of Toulon 1793 (Picture Post Library)

from the agony of spasm

Gastric and duodenal ulcer, spastic dysmenorrhœa, renal and biliary colic, these and many other painful spastic conditions will respond to the rapid, smooth action of BUSCOPAN. BUSCOPAN is a spasmolytic with a specific point of attack having an effect upon the hollow organs of the abdomen and genito-urinary tract. Safe and effective in all its uses, BUSCOPAN is virtually free from atropine-like side effects.

*BUSCOPAN**

HYOSCINE-N-BUTYLBROMIDE

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent for

C. H. Boehringer Sohn, Ingelheim am Rhein

* *Regd. Trade Mark*

Registered proprietors of the Trade Mark.

Is there a 'best' antibiotic for routine use in general practice?

In general practice the ideal method of selecting an antibiotic — laboratory determination of precise sensitivity — is often impracticable. It causes delays which may be dangerous and, applied consistently by every general practitioner, would grossly over-load available laboratory facilities.

In general practice, therefore, the need is for an antibiotic which clears almost all common infections, quickly, and with a minimum of undesirable side effects. Simplicity of dosage is an added advantage, particularly where administration must be left to relatives or parents.

The value of Sigmamycin*

oleandomycin tetracycline

in general practice

Over the whole range of infections susceptible to tetracycline Sigmamycin offers enhanced potency, producing faster and more complete eradication. Matromycin* (the Pfizer brand of oleandomycin) is an exceptionally well tolerated antibiotic. Its inclusion in Sigmamycin permits a reduction in the dose of tetracycline. Sigmamycin is, therefore, a carefully calculated combination of antibiotics designed to offer enhanced activity, improved tolerance, and a simple scale of dosage over the whole range of 'general practice' infections. The remarkable characteristics of this very successful combination have been amply demonstrated by extensive clinical trials.[1]

Dosage with Sigmamycin is unusually simple. Adults: moderate infections, one 250 mg. capsule every six hours; severe infections, two 250 mg. capsules every six hours. In overwhelming infections a further increase may be needed and may safely be given. Children: moderate infections, two 50 mg. capsules every six hours; severe infections, four 50 mg. capsules every six hours.

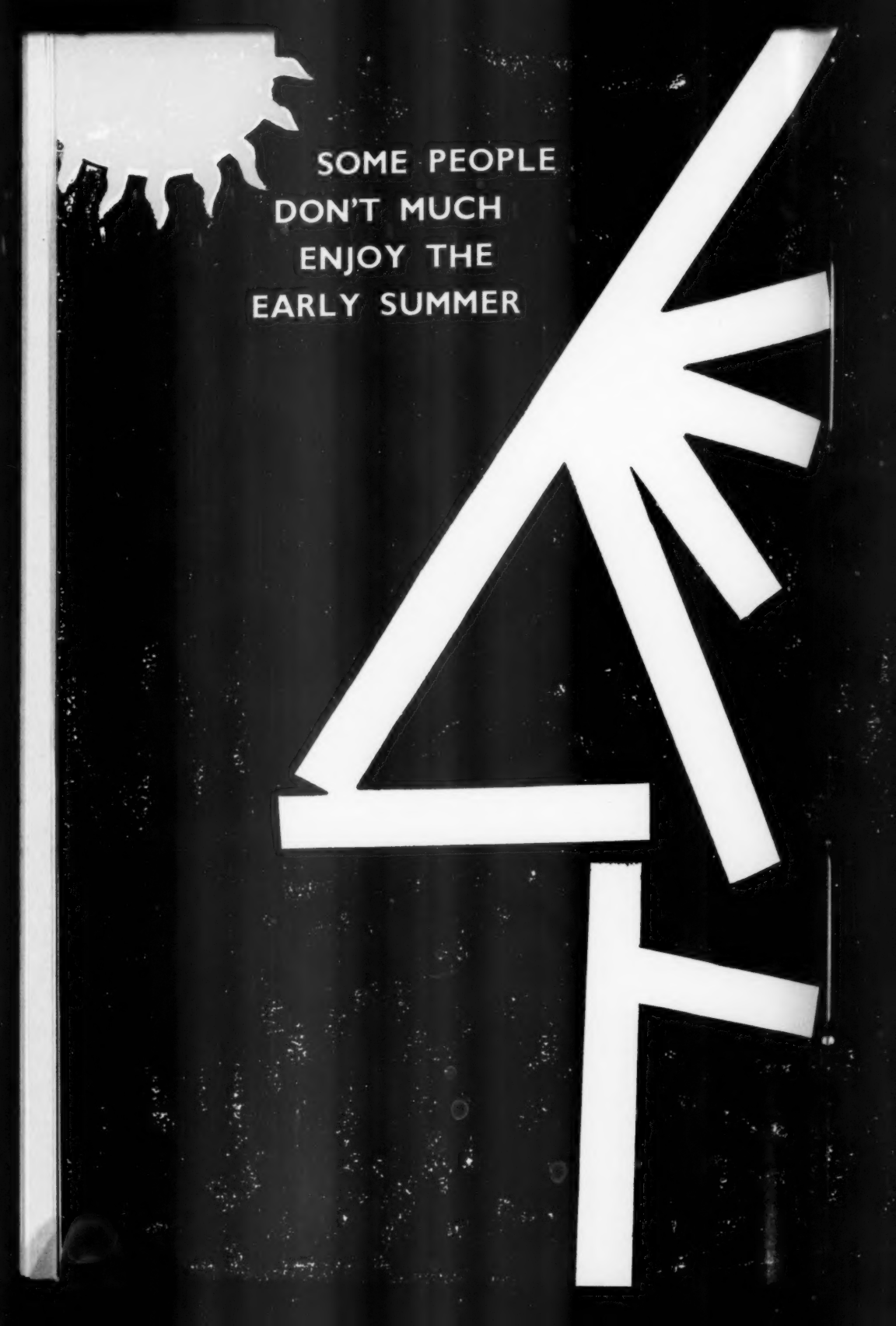
1 A full summary of current information on Sigmamycin, together with a review of clinical trials, is available upon application.

Sigmamycin 250 mg. capsules, each containing 167 mg. tetracycline and 83 mg. oleandomycin, are available in bottles of 16 and 100. Sigmamycin 50 mg. capsules each containing 33.3 mg. tetracycline and 16.7 mg. oleandomycin are available in bottles of 25 and 100.

Pfizer **World's largest producer of antibiotics**

PFIZER LTD · FOLKESTONE · KENT

*Trade Mark of Chas. Pfizer & Co., Inc.


SOME PEOPLE
DON'T MUCH
ENJOY THE
EARLY SUMMER

BECAUSE IT IS THE SEASON WHEN POLLEN IS IN THE AIR

As long as there is pollen in the air, usually for about six weeks in the early summer, the hay fever patient requires almost constant treatment. Cortril Snuff is a preparation well calculated to meet this recurring need. By presenting the remarkable anti-inflammatory and anti-allergic properties of hydrocortisone in the form of a powder suitable for insufflation, Cortril Snuff affords prolonged relief quickly and simply, and with the best possible chance of complete control.

. . . BUT IT IS ALSO THE

Cortril* Snuff SEASON

brand of hydrocortisone

Administration: Cortril Snuff capsules are suitable for use in a Powder insufflator. The capsule is pierced and inserted in the tube of insufflator. The tip is then inserted into each nostril and the bulb is squeezed and released once or twice in quick succession, distributing the powder over the nasal mucosa. This may be repeated several times daily. One capsule is normally sufficient for a day's treatment.

Packaging: Cortril Snuff capsules, each of which contains 15 mg. hydrocortisone free alcohol in 85 mg. lactose are available in bottles of five and twenty-five.

WHEN DECONGESTION IS NEEDED

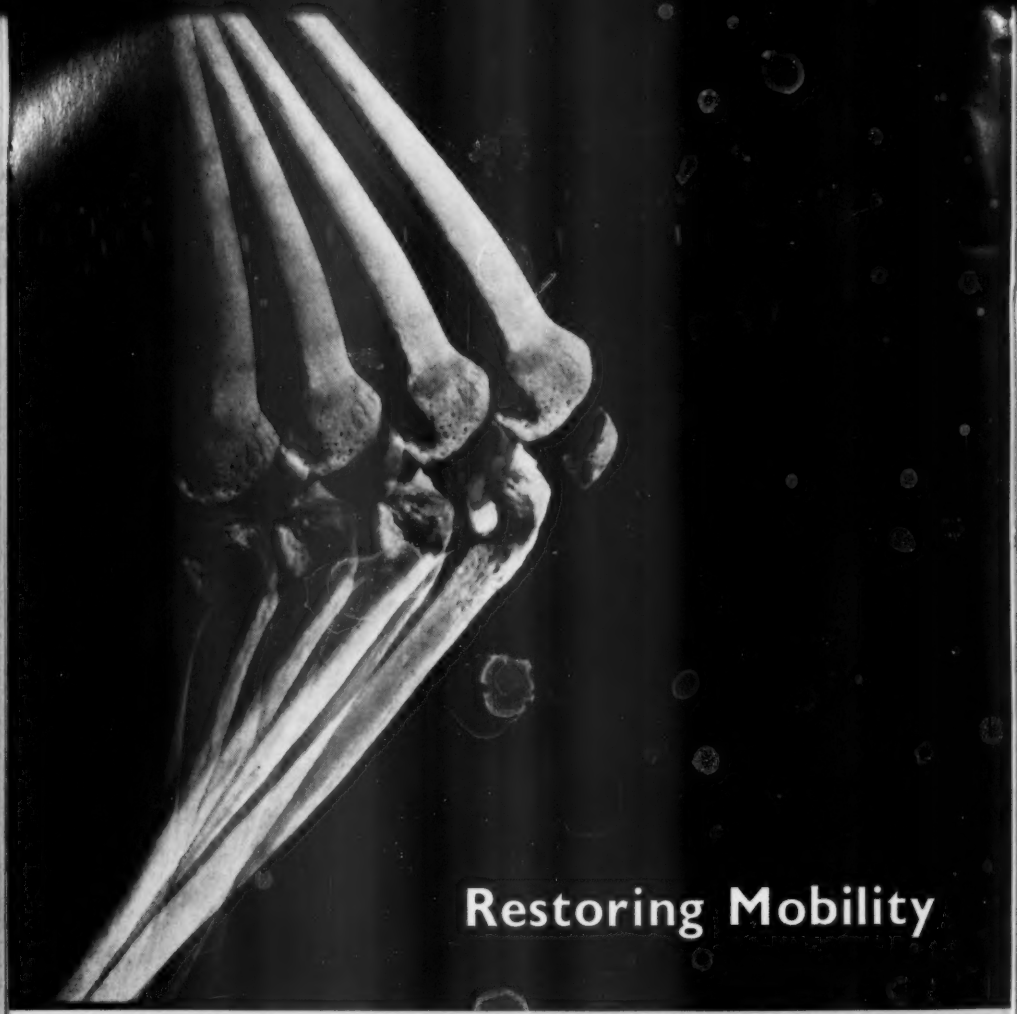
Frequently the nostrils and the nasal cavity must be cleared before satisfactory insufflation is possible. Tyzanol, which is an unusually safe and potent nasal decongestant, is strongly recommended for use on these occasions. Tyzanol is available in a 15 c.c. plastic squeeze bottle containing 0.1% tetrahydrozoline hydrochloride.

*Tyzanol**

brand of tetrahydrozoline hydrochloride

Pfizer PFIZER LTD · POLKESTONE · KENT

* *Trade Mark of Chas. Pfizer & Co., Inc.*



in severe rheumatoid arthritis

Deltacortril*

brand of prednisolone

"... more effective than any previous drug in the control of the signs and symptoms of rheumatoid arthritis." *Lancet* (1955) ii, 1393

Tablets containing 5 mg. prednisolone in bottles of 10, 20, 100, 500, and 1,000. Tablets containing 1 mg. prednisolone in bottles of 100.

in less severe rheumatoid arthritis

Deltalgycortril*

prednisolone and acetylsalicylic acid

"Four hundred cases of various types of arthritis were treated ... with notable improvement and with a minimum of side effects." *Ohio State Med. J.* (1956) 52, 722

Each tablet contains 0.5 mg. prednisolone and 5 grains acetylsalicylic acid. Available in bottles of 100.

Pfizer PFIZER LTD · FOLKESTONE · KENT

* *Trade Mark of Chas. Pfizer & Co., Inc.*

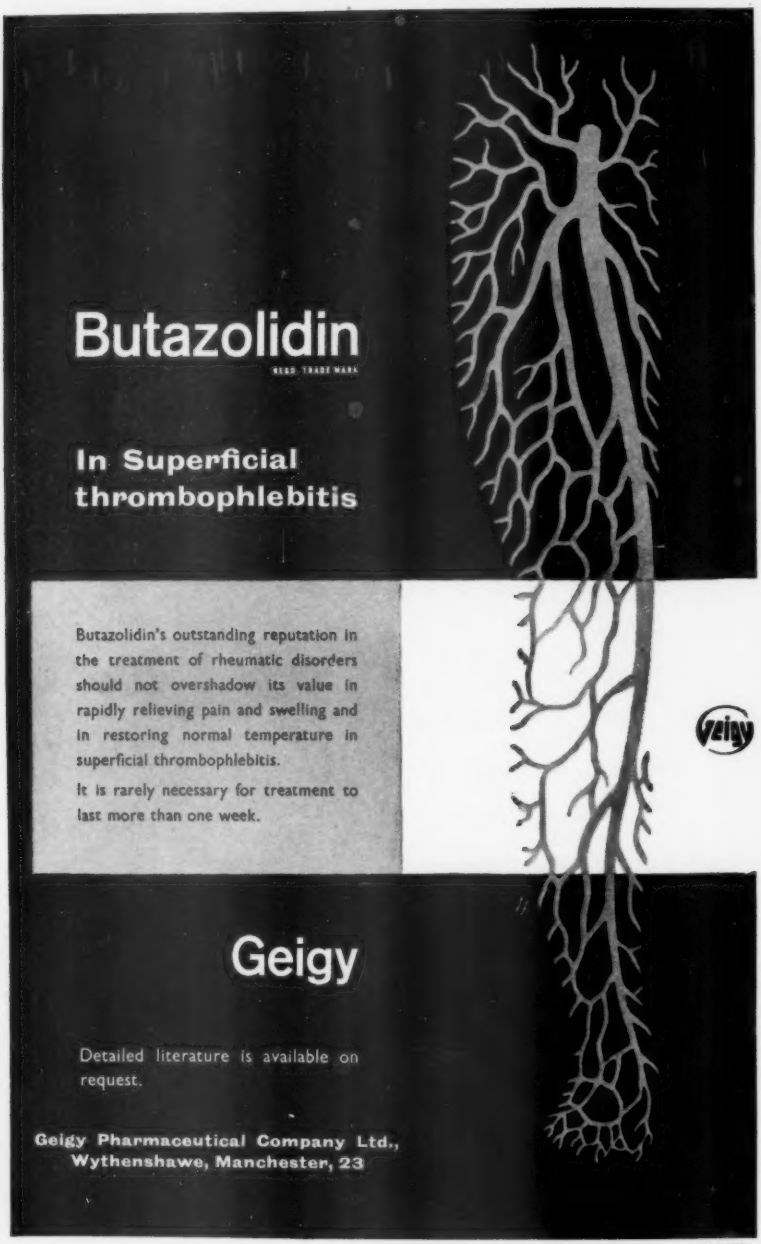
dieting needs determination

Keeping rigidly to a prescribed diet is generally more easily said than done since many obese patients, while anxious to lose weight, have not the will to resist the craving for food.
PRELUDIN removes the desire to overeat and enables the patient to co-operate effortlessly in any prescribed weight-reducing plan. In cases of obesity coupled with cardiovascular disorders or hypertension Preludin is always the safe prescription since it affects neither the heart nor the blood pressure.
PRELUDIN *is supplied in tablets of 25 mg. each, packed in tubes of 20 or bottles of 250.*

PRELUDIN*

2-phenyl-3-methyl-tetrahydro-1, 4-oxazine-hydrochloride

Manufactured and distributed in England by Pfizer Ltd., Folkestone, Kent, for
C. H. Boehringer Sohn, Ingelheim am Rhein
*Registered proprietors of the Trade Mark. * Regd. Trade Mark*


Butazolidin
REGD. TRADE MARK
In Superficial thrombophlebitis
Butazolidin's outstanding reputation in the treatment of rheumatic disorders should not overshadow its value in rapidly relieving pain and swelling and in restoring normal temperature in superficial thrombophlebitis.
It is rarely necessary for treatment to last more than one week.
Geigy
Geigy
Detailed literature is available on request.
Geigy Pharmaceutical Company Ltd., Wythenshawe, Manchester, 23

PH.103a.

Iron your patients can tolerate...

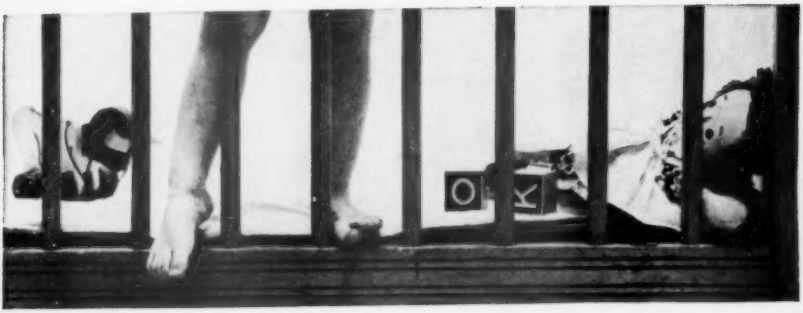
Rarical

iron-calcium tablets

Ortho

Ortho Pharmaceutical Limited

High Wycombe · England



IN CHILDREN . . .

THE 'ESKACILLIN' RANGE

of palatable LIQUID oral penicillins

The 'Eskacillins' are particularly acceptable to children. When a sore throat makes it difficult for the child to swallow tablets or capsules, the liquid form is easy to take; if he is petulant and unco-operative the carefully balanced flavour eliminates nose-holding and gagging, which may dissuade parents from giving correct dosage.

ESKACILLIN | 100 200 300

palatability—flexibility of dosage—rapid action

SMITH KLINE & FRENCH LABORATORIES LTD
Coldharbour Lane, London SE5

'Eskacillin' is a trade mark

ECP36 (col)

The esters of NICOTINIC, SALICYLIC and p-AMINOBENZOIC acids

bring relief to cases of arthritis and rheumatism

In cases of soft-tissue rheumatism, and arthritic disorders, many doctors are tending more and more to regard Transvasin as an indispensable adjuvant to treatment.

For Transvasin is composed of the esters of nicotinic, salicylic and p-aminobenzoic acids. These esters readily pass the skin barrier in therapeutic quantities, and so enable an effective concentration of drugs to be built up where they are needed.*

Transvasin not only induces vasodilation of the skin with a superficial erythema, but also brings about a deep hyperaemia of the underlying tissues. It is non-irritant and can be safely used on delicate skins.

It is now being widely prescribed, with successful clinical results. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

* *Therapeutische Umschau VIII, 1952, 10, 143.*

In 1 oz. tubes, basic N.H.S. price in the U.K. 2/6 plus P.T. May be prescribed on Form E.C.10.

Salicylic acid tetrahydrofurfuryl-ester	*14%*
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LLOYD-HAMOL LTD

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"Thank you, doctor"

Transvasin is the registered trade mark of Lloyd-Hamol Ltd.

DYSMENORRHOEA

The incidence of recurring sickness among 7,735,000 women in industry would be greatly alleviated by an improved dysmenorrhoea therapy

Femerital
BRAND DIBUTAMIDE

A SPECIFIC THERAPY FOR DYSMENORRHOEA

It is difficult to obtain an accurate estimate of the incidence of dysmenorrhoea in women working in industry. Consideration of the voluminous literature on this subject is confusing: the estimated incidence varies between 3% and 90%. It is fairly universally agreed however that dysmenorrhoea is an important cause of recurrent sickness although the magnitude of this cannot be precisely specified.

The aetiological factors involved in primary dysmenorrhoea are numerous, but it appears that the immediate cause of pain is ischaemia due to uterine muscle spasm. The state of general health and psychological factors play an important part in the causation of the condition, but it is often difficult to define these abnormalities and correct them.

Attendance to nutrition, exercise and emotional disturbance are important parts of management, but in addition it is essential to relieve uterine spasm, reduce sensitivity to pain and elevate mood. Femerital was compounded to meet these requirements. The preparation contains Dibutamide, a new and specific uterine antispasmodic, the action of which is unattended by side reactions such as hypotension and constipation. Salicylamide and phenacetin are included for the central relief of pain, and caffeine for its mild diuretic and stimulant effects.

Clinical trials in over 1,000 cases have proved the efficiency of this combination, good results being obtained in over 75% of cases.

Manufactured and distributed by

M.C.P. PURE DRUGS LTD., 86 STRAND
LONDON. W.C.2

From milk to mixed diet

HOW HEINZ STRAINED FOODS HELP

Mothers of three or four-month-old babies often need your practical advice about how to start baby on a mixed diet.

When you suggest Heinz Strained Foods you can do so with complete confidence. The 19 different foods, introduced gradually from about three-months onwards, between them offer scope for a varied diet. They are cooked and strained under strictly controlled conditions, with the minimum loss of food values. And, of course, they are prepared much more hygienically than they would be in an ordinary kitchen.

For full details of the nutrient values of the 19 varieties of Heinz Strained Foods, write to Dept. T7, H. J. Heinz Co. Ltd., Harlesden, London N.W.10.

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Strained Foods

MEAT BROTHS · SOUPS · VEGETABLES · SWEETS · CEREAL

One drop spreads multiple benefits

INFLAMMATION WITH INFECTION DEMANDS

'HYDELTRACIN'

TRADE MARK

WHEN A SKIN LOTION IS PREFERRED

Prednisolone when applied to skin lesions, exerts anti-inflammatory, anti-allergic and anti-pruritic actions similar to hydrocortisone—but concentrations only one-fifth to one-half that of the parent steroid are required. 'Hydeltracin' Topical Lotion contains 0.5 per cent of prednisolone together with 0.5 per cent of neomycin sulphate. The inclusion of neomycin ensures effective attack on most pathogenic organisms commonly found in skin lesions, and is necessary when prednisolone is used locally in the presence of infection. 'Hydeltracin' is indicated in skin lesions characterised by inflammation, with or without infection, such as: seborrhoeic dermatitis, contact dermatitis, adult eczema, infantile eczema, pruritus with lichenification, otitis externa, intertrigo.

NEW Topical Lotion—Prednisolone with Neomycin

How supplied:

'Hydeltracin' Topical Lotion is formulated in an elegant, non-greasy base, and packed in plastic squeeze-bottles containing 15 ml.

MSD MERCK SHARP & DOHME LIMITED, HODDESDON HERTS

Working for the Nation's Children No. 8

A Soldier's Farewell

After more than thirty years as a soldier and another twenty during which I served in the uniform of an Inspector of the N.S.P.C.C., I am retiring.

For me, I suppose, it's been more or less fighting all the way—first as a soldier in two world wars and then in the war the N.S.P.C.C. is constantly waging against the cruel treatment and neglect of children.

I have been able to help over 5,500 children in my time, many of whom I shall never forget. They went through hell before I was called in. Poor kids, if I had been told of their plight earlier, I could have done so much more to help them.

So this is my farewell message to you all—if you ever do hear of a child in trouble, let the N.S.P.C.C. know at once. You will save it from so much misery and suffering. Goodbye and God bless you !'

T. B. N. BRIDGER

The scope of the Society's work is very much wider than dealing with cases of cruelty or gross neglect. If the Society can do anything at any time to help children whose welfare, happiness or future is in jeopardy, it will do it. This vital humanitarian work depends on your subscriptions and support. Please send your contributions to:

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The N.S.P.C.C. helped nearly 100,000 children last year

When advising on wills and bequests remember the N.S.P.C.C.

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"Eupinal" contains Iodine and Caffeine combined in a most elegant and effective form.

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Vitamin deficiencies can result in frank psychiatric disorders; the dementia of pellagra is the classical example of this effect. Less well-defined deficiencies, particularly of the vitamin B group, are occasionally associated with other psychiatric conditions, such as the mental sequelæ of virus infections, heavy barbiturate sedation or continuous clinical narcosis. While acute deficiencies are treated by parenteral administration of massive doses of vitamins, increased oral intake is a more convenient form of long-continued maintenance therapy.

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MARMITE *Literature on request*

yeast extract

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and they can keep it down—

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LUCOZADE

the sparkling glucose drink

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Methyl Nicotinate 1.0%
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INDICATIONS:
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Taken at the onset of asthmatic attack, Isoprenaline Sulphate in RESPEDRINE aborts the spasm and dilates the bronchioles, producing immediate relief.

To maintain this relief, RESPEDRINE contains two slower but longer-acting drugs—Ephedrine and Theophylline. A small amount of Phenobarbitone is included for sedation, and counteracts the stimulant action of Ephedrine.

- **Vital capacity of the lungs is increased.**
- **Two-in-one tablet giving immediate relief sustained for several hours.**
- **Does not have any stimulating effect.**
- **Packs 100's 12s., 500's 55s.**

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Isoprenaline Sulphate	*15 mg.*
Ephedrine Hydrochloride	*15 mg.*
Theophylline	*130 mg.*
Phenobaritone	*8 mg.*

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Hay Fever

* treated successfully with

Hydrocortisone Acetate
SNUFF CAPSULES

* for use in the Armour Insufflator

Designed and patented by Armour and Company British Patent No. 668341

Supplied as Hydrocortisone Acetate Insufflation Set, consisting of one Insufflator and 6 capsules each containing 15 mg. Hydrocortisone Acetate Snuff with inert substance. Also refills in bottles containing 6, 12 and 25 capsules.

Reference :
LANCET i (1956) 537

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FOR NEURASTHENIA AND ANXIETY STATES

This pleasantly flavoured elixir contains Phenobarbitone together with Vitamins B1, B2, B6 and Nicotinamide. Ideally suited for the treatment of various conditions associated with the B complex deficiencies such as general fatigue, anorexia, gastro-intestinal disturbances, tachycardia, irritability and depression.

FORMULA: Phenobarbitone B.P. ¼ grain, Aneurin Hydrochloride B.P. 1.5 mgm., Riboflavine B.P. 1.0 mgm., Pyridoxine Hydrochloride B.P.C. 0.17 mgm., Nicotinamide B.P. 10 mgm., Glycerin B.P. 42 minims, Alcohol B.P. 9 minims, Colour and flavour a sufficiency, Base to 1 fluid drachm.

POISON | S1 | S4

PRESENTATION: In screw-capped bottles: 5 fl. ozs. 5/10; 20 fl. ozs. 21/8; 80 fl. ozs. 76/10; Subject to professional discount.

Dispensing packs exempt from purchase tax.
Samples available on request.

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WB1

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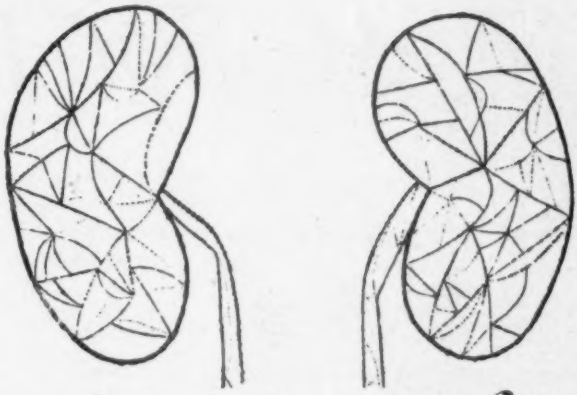
WRIGHT'S COAL TAR SOAP IN TOILET AND BATH SIZES



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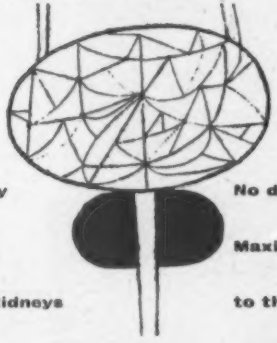
for sustained, specific, safe therapy of

chronic urinary infections



High antibacterial potency

Minimal side effects

No crystallization in the kidneys

No drug resistance

Maximum convenience to the patient

Each Hafgram tablet contains 0·5 g. (gr. 7½) Methenamine (hexamine) mandelate

In bottles of 30 · Samples and literature on request

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M:PA17

'Mandelamine' is the registered trade mark of Nepera Chemical Co. Ltd.

'Miotrol'-P

TRADE MARK

A synergistic combination of androgen and oestrogen with phenobarbitone. Specifically designed for control of symptoms associated with menopausal disturbances, premenstrual migraine and tension, dysmenorrhoea.

FORMULA: *Methyl Testosterone 2.5 mg.*
Ethinyl Oestradiol 0.005 mg.
Phenobarbitone 16.0 mg. (¼ gr.)

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LITERATURE FORWARDED ON REQUEST

AN OXOID PRODUCT

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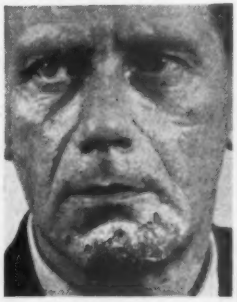

Diagnosis: Obstinate eczema of the face. Photograph taken before treatment with "F99."

Photograph taken after 11 weeks' treatment with one "F99" capsule and one application of "F99" ointment daily.

F99 for

OINTMENT
CAPSULES
LIQUID

ECZEMA
VARICOSE ULCERS
FURUNCULOSIS

It has been shown beyond question by large scale serum-lipids studies that a good proportion of patients suffering from intractable skin conditions have a deficiency of the essential fatty acids. It is not possible to carry out these studies in everyday practice, but any patient with eczema or furunculosis who fails to respond to symptomatic treatment should most certainly be tried with essential fatty acids "F99." A high proportion of these patients will be found to respond.
In gravitational ulcers, where the skin is "under-nourished," the application of additional essential fatty acids rarely fails to heal the wound.

Literature on request

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Equanil

RESTORES REPOSE

When repose is a requisite

Anxiety is frequently a contributing factor in physical sickness, particularly when the gastro-intestinal tract is involved, for it so often acts as the sounding board of the emotions. Frustrations, arising from such things as limitations in diet, and fears engendered by the complaint itself may quickly aggravate the patient's symptoms, which, in turn, may intensify his anxiety. And so is set in motion a vicious spiral of sickness—a threat to progress; a barrier to repose.

Equanil acts as a brake; a regulator on the main spring of the patient's nervous system. By its selective action on the thalamus and the cortex, Equanil produces relaxation of both mind and muscle. It restores repose and helps the patient to regain his sense of proportion.

Equanil *the safe, reli*

(MEPROBAMATE)

PACKS: Bottles of 20 and 250 × 400 mg. tablets

The word 'Equanil' is a registered trade mark

Wyeth

ble and effective anti-anxiety agent

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Many people live a life of quiet depression behind a mask of forced gaiety. For them treatment with Mephine can offer new hope and a brighter outlook on life. Mephine smoothly and safely ameliorates the depressed patient's mood, quickly replacing their apathy and lethargy with renewed interest and drive. And it does so without undesirable excitation or appetite loss.

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(MEPHENTERMINE SULPHATE)

ELIXIR AND TABLETS

An important new agent to dispel depression

SUPPLIES: Elixir in bottles of 2 fl. oz. (each 4 c.c. teaspoonful contains 10 mg. mephentermine sulphate). Tablets in tubes of 20 × 10 mg.

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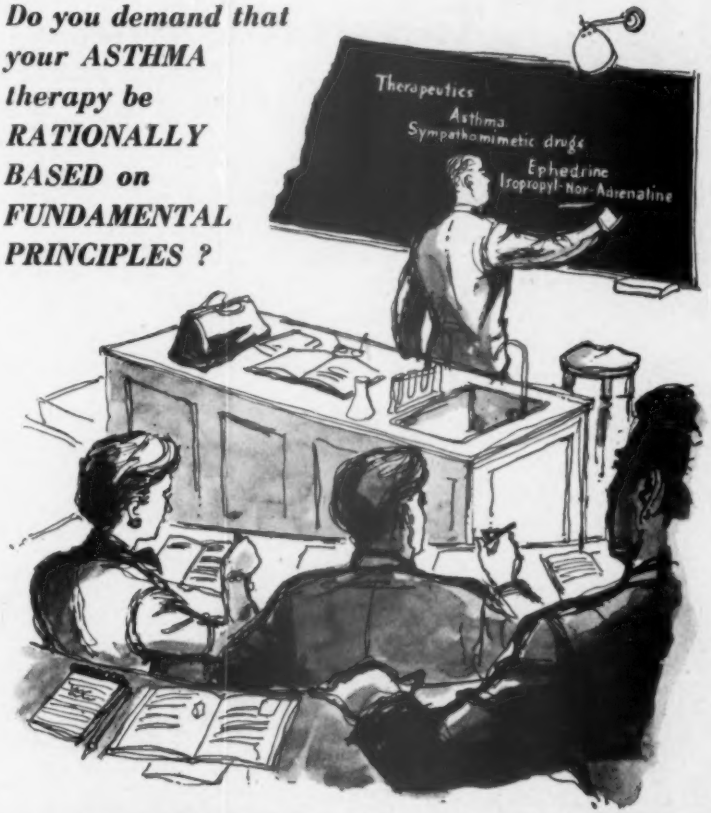

ISO-BRONCHISAN was first produced in 1953 and its modus operandi in bronchial asthma demonstrates that, as in education so in therapy, the best is rationally based on fundamental principles. The outer layer of the Iso-Bronchisan tablet, containing Isoprenaline, is quickly absorbed from beneath the tongue affording rapid relief from bronchospasm. The core, containing ephedrine and theophylline, is then swallowed and slowly absorbed with a resulting sustained bronchodilation, thus combining well established immediate and long acting bronchodilators in one tablet. **Prescribable on E:C.10.**

Each Iso-Bronchisan tablet contains		
	Isopropyl-Nor-Adrenaline (Isoprenaline) sulphate	gr. ¼
	Ephedrine hydrochlor.	gr. ¼
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(Special tablets available for children.)

Samples and literature available on request from

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When the Mediaeval King put aside his arms and stood alone, coldly footing it in chilly castle chamber, why the frowning concern with hair? Was it the scalp worry of all ages? Dandruff?

Sebaceous glands being the secretory things they are, there was then no royal remedy for the regal irritation. But today the old and familiar trouble has been mastered by SEBODERM, the Cetrimide Shampoo specifically for Dandruff.

Seboderm contains 15.6% of Cetrimide B.P., the quaternary ammonium prescribed as most effective against dandruff. Normally a single weekly treatment is sufficient to establish complete control.

Seboderm also contains 15.6% Cetyl Alcohol B.P. and 1% Lanolin, and as a finely emulsified, creamy shampoo it leaves the scalp free from irritation and the hair soft, silky and clean

Seboderm masters Dandruff

Professional sample will be gladly sent on request

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WEST DRAYTON MIDDLESEX

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—and brings you a full

4% TAX FREE

Equal to £6. 19. 2 PER CENT GROSS
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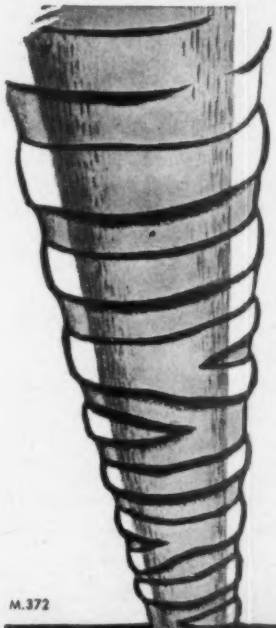

Relieving the bronchial tree in asthma

'ASMAC' TABLETS are formularized to provide symptomatic relief of the bronchial tree both during actual dyspnoeic attacks of bronchial asthma, and during remissions.

'Asmac' Tablets combine in a single prescription 'official' drugs recognized for their reliability to effect mental sedation, decongestion, expectoration and bronchodilatation.

PACKS AND COST TO PHARMACISTS

Standard Tube of 20: 3/-.
Dispensing Bottles: 100, 12/-; 500, 52/6; 1,000, 102/6.

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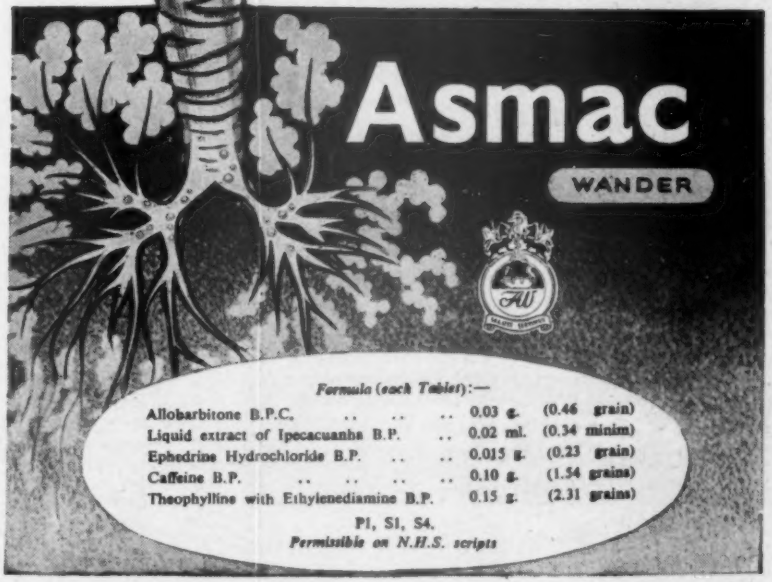
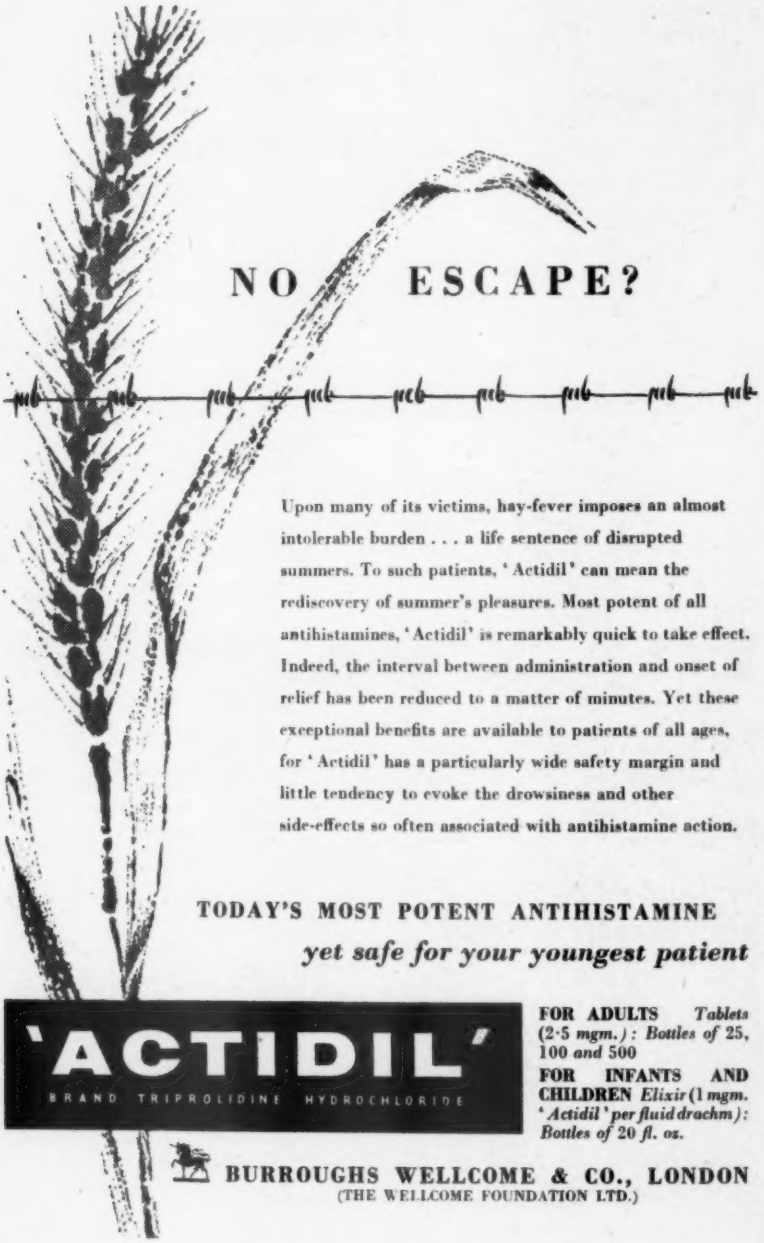


Formula (each Tablet):—

Allobarbitone B.P.C.	0.03 g.	(0.46 grain)
Liquid extract of Ipecacuanha B.P.	0.02 ml.	(0.34 minim)
Ephedrine Hydrochloride B.P.	0.015 g.	(0.23 grain)
Caffeine B.P.	0.10 g.	(1.54 grains)
Theophylline with Ethylenediamine B.P.	0.15 g.	(2.31 grains)

PI, SI, S4.
Permissible on N.H.S. scripts



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Upon many of its victims, hay-fever imposes an almost intolerable burden . . . a life sentence of disrupted summers. To such patients, 'Actidil' can mean the rediscovery of summer's pleasures. Most potent of all antihistamines, 'Actidil' is remarkably quick to take effect. Indeed, the interval between administration and onset of relief has been reduced to a matter of minutes. Yet these exceptional benefits are available to patients of all ages, for 'Actidil' has a particularly wide safety margin and little tendency to evoke the drowsiness and other side-effects so often associated with antihistamine action.

TODAY'S MOST POTENT ANTIHISTAMINE

yet safe for your youngest patient

'ACTIDIL'

BRAND TRIPROLIDINE HYDROCHLORIDE

FOR ADULTS *Tablets (2·5 mgm.): Bottles of* 25, 100 *and* 500

FOR INFANTS AND CHILDREN *Elixir (1 mgm. 'Actidil' per fluid drachm): Bottles of* 20 *fl. oz.*

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IT WAS RECENTLY reported (*Brit. med. J.*, 1: 444, 1957) that of 178 rheumatic patients, 25% could not take plain aspirin in adequate dosage.

Of this 25%, however, the great majority tolerated a modified aspirin such as Paynocil.

Not only are Paynocil tablets usually well tolerated by the stomach (even on the heavy dosage needed for rheumatoid arthritis), but they are extremely palatable, disintegrate instantly on the tongue without water, and cause no discomfort or unpleasant after-sensation.

...indicates PAYNOCIL

non-irritant, palatable, quick-dispersing aspirin

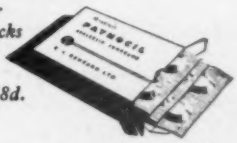
FOR ADULTS

PAYNOCIL

EACH TABLET CONTAINS

Acetylsalicylic acid ..... 10 grains
Aminoacetic acid ..... 5 grains

PACKAGES in sealed foil strips:
Cartons of 18.
Dispensing packs of 240: basic N.H.S. cost (tax free) 21/8d.



FOR CHILDREN

Junior PAYNOCIL

EACH TABLET CONTAINS

Acetylsalicylic acid ..... 2½ grains
Aminoacetic acid ..... 1½ grains

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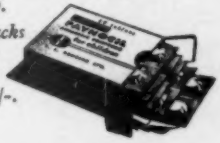
Cartons of 20.
Dispensing packs of 240: basic N.H.S. cost (tax free) 12/-.



Detailed recommendations for dosage in rheumatoid arthritis will be gladly supplied on request

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THE PRACTITIONER

No. 1068 JUNE 1957 Volume 178

THE MONTH

The Symposium

Of all the many medical terms which trip off the tongue of the layman today, none is more abused than 'allergy'. It has become almost as meaningless in its connotation as 'neurasthenia' a generation ago, and 'rheumatism' in the advertisements of the lay press. The profession has been almost equally careless in its use of the term, and for too long 'allergy' has been the dumping ground of all those diseases for which no etiology could be found. The number of unfortunate children, for instance, who have been deprived of many of the pleasures of the tea-table because their parents, or doctor, considered them to be 'allergic' to some particularly delectable delicacy must be nearly uncountable. Fortunately, all this time the experts—both clinical and laboratory—have been steadily pursuing their investigations, and we are now beginning to be able to sort out the tangled skein. The complex story is admirably unravelled in Professor Payling Wright's introductory article in our symposium this month. The other articles, by experts at home and abroad, deal with those aspects of the subject which are of most interest to the practitioner. Much has been learnt of recent years. The final elucidation of the problem depends, as Professor Payling Wright points out, 'upon close collaboration between laboratory workers engaged upon experimental immunological studies of a fundamental character and clinicians who are prepared to study and apply their findings to the analysis of these obscure syndromes'.

Measuring Morbidity

As the social standards of a country rise the emphasis shifts from mortality to morbidity. In other words, the 'struggle for existence' becomes the striving for healthy living. In the achieving and maintenance of such healthy living, statistics are essential, particularly in the highly complex society which the modern Welfare State has become. As Dr. B. Benjamin, of the General Register Office, pointed out recently in a paper on 'The measurement of morbidity' which he read before the Institute of Actuaries, the collection of morbidity statistics is much more difficult than that of mortality statistics.

The fundamental problem was admirably epitomized by Dr. Percy Stocks some years ago: 'The distinction between living and dead is clear-cut, but no such frontier line between sickness and health can be said to exist . . . There is a zone between the two states in which the division whether the subject is sick or not depends on definitions or standards of good health, and also on who decides'. Not only is there the difficulty in defining the 'normal'—and Dr. Benjamin quotes ranges of normality which are a nightmare to the statistician—but in determining the data upon which morbidity

statistics are to be based. Sickness absence can only be accepted with reservations as a criterion. To quote Dr. Benjamin: 'The point of time at which an employed person "goes sick" may depend not only on the absolute fact of feeling unwell but on whether there is any loss of income involved . . . Even for non-employed persons a similar difficulty arises; a housewife with a large family and unable to afford assistance may struggle to carry on longer than those with less responsibility and more domestic help'. Even though a medical certificate may be available 'the need to submit the medical certificate to an employer may tend to make the medical practitioner circumspect in his description of the condition causing incapacity'. It may well be that in the end general practitioners' records may provide the most reliable data. It is for this reason that so much importance attaches to the forthcoming report of the morbidity survey, covering a population of 400,000, carried out by the College of General Practitioners in collaboration with the Registrar General's Department.

William Harvey

WITH due pomp and ceremony the learned medical societies of the country are about to commemorate the tercentenary of the death of William Harvey, which occurred on June 3, 1657. The pomp and ceremony, however, will only be part of the tercentenary congress. The greater part of the commemorative week is to be devoted to a review of the progress made in our knowledge and understanding of the circulation of the blood since the publication of Harvey's classic, 'Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus'. This is as Harvey himself would have wished. He was the father of rational physiology, and nothing would have given him more pleasure than to know that this tercentenary commemoration would not take the form of mere adulation but would be the occasion for assessing our current understanding of the circulation of the blood in the light of the immortal 'De Motu Cordis'. And if there be reasoned criticism of his work, no-one would have welcomed it more than Harvey because, as Dr. Louis Chauvois points out in his fascinating new study of him ('William Harvey, His Life and Times: His Discoveries: His Methods'. London: Hutchinson Medical Publications. Price 25*s*.), Harvey was always the first to admit that his views might require modification in the light of subsequent investigations.

Harvey's work and reputation are international, but we in this country have a special interest in him, not only because he was born in this country, but also because of the great British school of cardiology, which owes its origin and being to Harvey's inspiration. It is a school which has added lustre to the annals of medicine throughout the three centuries that have elapsed since Harvey's death. Not the least of its claims to fame is the emphasis it has always laid upon the art, as opposed to the science, of medicine. And here it is in the true Harveian tradition. Harvey was no academic research worker blinkered to a line of vision which took in only the laboratory bench. He was first and foremost a physician, a practitioner of the healing art. It was not for the sake of pure knowledge that he studied

the circulation of the blood but in order that from the knowledge so acquired he might be better able to bring solace and relief to his patients. It is thus as a clinician, as well as, in Dr. Chauvois' words, one of 'the three or four master intelligences of all time', that this month we commemorate the memory of William Harvey.

Comics to Classics

FIFTY per cent. of the population in this country read no books at all, 12 per cent. read a great deal, 25 per cent. a fair amount and the rest very little. Such are some of the facts that were brought out at a Conference on Children's Reading last November, the report of which has now been published ('From Comics to Classics'. Copies, price 2*s*. 2*d*. post free, can be obtained from the conference secretary, Mrs. Anthea Holme, 23 Marlborough Place, London, N.W.8). Whilst the subject is of primary interest to the educationist, it is one which must also be of interest to all doctors concerned with the welfare of the children in their practices.

The 'horror comic' has never been such a problem in this country as in the United States. What is disturbing about British 'comics' is their low cultural standards and the extent to which they tend to monopolize the reading time of children. One speaker, for instance, told of the secondary modern school at which he works: 'When I first went to the school, you could hardly see the school for comics. They were stuffed down boys' sweaters, they filled wastepaper baskets—where irate teachers had put them: they were everywhere'. It was at this same school that one effective way was discovered of driving out the 'comic'—the introduction of a school library. No-one wishes to deprive the modern child of his 'comics', even though there are many who will agree with the director of the institute of education in the University of Nottingham, that it is 'difficult to believe that reading comics is completely harmless'. The main criticism of them is their low level of taste. The problem to which no solution has yet been found—though many partial solutions are discussed in this interesting report—is how to provide the right reading material for the semi-literate populace with which we have been presented as a result of eighty years of universal education.

American Leeching

IN these days when new drugs are two a penny, and doctors who do not prescribe the latest drug recommended by the Sunday press are considered old-fashioned by their patients, it is refreshing to find an American medical journal devoting space to an article recording the first case of severe iron-deficiency anæmia resulting from leeching to be reported in the American literature. Whether or not the claim to priority will be substantiated by the experts remains to be seen, but the case, which is reported by Seymour Glick and Norton D. Ritz (*New Engl. J. Med.*, 1957, **256**, 409), is of more than passing interest.

A 67-year-old Sicilian-born lady was admitted to a New York hospital on account of gross anæmia and congestive heart failure. Her history was that for three to five years she had been applying one to three leeches to her skin or mucous membrane daily for miscellaneous complaints. If her eyesight was

bad, she applied leeches round her eyes. For toothache she applied them to her gums, and when her skin itched she applied them to the pruritic areas. Apparently she withdrew up to a glassful of blood at a single leeching. On admission she was found to have a red-cell count of only 1,750,000 per c.mm. and a hæmoglobin of 3.9 g. per 100 ml., with signs of congestive heart failure. The response to treatment was satisfactory, and when seen three months after discharge the red-cell count was 4,200,000 per c.mm. and the hæmoglobin was 14.5 g. per ml. With true Sicilian obstinacy, however, she was still clinging to her leeches 'although more moderately than previously'. We feel that somewhere in this tale from New York is hidden a moral upon which the medical philosopher should be able to seize. It is not so very long ago since Alton Ochsner was quoted as saying that if he had a coronary thrombosis he would 'want them to cover me with leeches'. Æsthetically displeasing though they may be, they probably carry fewer toxic hazards than the man-produced anticoagulants.

Surgeon Smollett

In the eighteenth century the easy way into the medical profession was to become a surgeon's mate in His Majesty's Navy. Service standards in such matters were low, and on retirement—after no matter how short a term of service—no restraint was placed on engagement in civilian practice. This was how Tobias Smollett gained admission to the profession—and on the lowest rung of the professional ladder—'second mate of a third rate'. Later—after a relatively short naval career—he obtained his Doctorate of Medicine from Aberdeen and set up residence for a time in Downing Street. There seems to be little doubt that it was the rich wife whom he had married while on service in the West Indies who paid for this standard of living—and not the money he made in the practice of medicine.

Hitherto the identity of the examiners who were responsible for admitting him as 'second mate of a third rate' has not been known. A note published in the *Annals of the Royal College of Surgeons of England* (1957, **20,** 260) now reveals that these were William Petty, surgeon-extraordinary to the London Hospital; James Ferne, surgeon 'for stone' to St. Thomas's Hospital; Claudius Amyand, surgeon to St. George's Hospital; and the great William Cheselden. If the account of the examination given in 'Adventures of Roderick Random' is based upon Smollett's own experiences, then it is to the kindness of Cheselden ('a plump gentleman with a skull before him') that Smollett owed his success. Whatever the vicissitudes of his life, Smollett retained his sense of humour to the end. This same note contains an excerpt from one of the last letters he wrote. It is to John Hunter and is dated January 9, 1771 (eight months before his death): 'If I can prevail upon my wife to execute my last will, you shall receive my poor carcase in a box, after I am dead, to be placed among your rarities. I am already so dry and emaciated, that I may pass for an Egyptian mummy, without any other preparation than some pitch and painted linen; unless you think I may deserve the denomination of a curiosity in my own character'.

THE CURRENT CONCEPT OF HYPERSENSITIVITY

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THE term 'hypersensitivity', which in recent years has become virtually synonymous with 'allergy', is now reserved for those clinical conditions in which the exaggerated response that follows from repeated exposure to some agent depends for its pathogenesis upon some immunological reaction that takes place in the affected structures between the provocative antigen and its specific antibody.

THE MECHANISM OF SERUM SICKNESS

Although the clinical features of hay fever and asthma, as well as the nature of some of the agents that excite them, had become widely known by the middle of the last century, it was only towards its close, and largely as a result of the greatly increasing use of antitoxin for the treatment of diphtheria, that the graver reactions of hypersensitivity emerged as problems of major importance. In the early days of specific therapy, large inoculations of crude horse serum obtained directly from highly immunized horses were administered to children with this disease, and it was the frequency with which these injections were followed by severe and sometimes fatal sequelæ that led von Pirquet and Schick to undertake their classical investigations on the nature and cause of the newly described 'serum sickness'.

Two circumstances favoured these Viennese pædiatricians in their analysis of this nosocomial disease: the high incidence of diphtheria in that city at that time, and the rapid advances in the fundamentals of immunology that were taking place currently under Ehrlich, von Behring and Gruber in the German and Austrian medical schools. Of both they took full advantage. Their clinical descriptions of the lymphadenitis, urticaria, arthralgia and pyrexia, which form the main elements in the syndrome of serum sickness have never been surpassed. But of greater significance for medicine generally, and for hypersensitivity in particular, was the perspicacity with which they unravelled the pathogenesis of this condition and linked it with the classical concepts that were then emerging in the new science of immunology.

Whilst an immense amount of patient study has been devoted to the analysis of hypersensitivity as an immunological state, the main principles that underlie the phenomenon were brought to light comparatively early and may be set out in relatively simple terms. The introduction of any protein, homologous or heterologous, into the tissues is promptly followed by its incorporation in the protoplasm of many different types of cell.

Much light has been thrown recently on the distribution and fate of such proteins through the employment of specific antibodies to which the dye, fluorescein, has been coupled chemically. The sites of deposition of the foreign protein in various tissues can be displayed very elegantly by exposing frozen histological sections first to the dye-coupled antibody and later to microscopical examination in ultra-violet light. In such preparations any place where the antigen has accumulated fluoresces brilliantly in the field of the microscope.

Studies employing this fluorescent technique have hitherto been few, but those that have been made have disclosed very clearly that the injected protein becomes deposited in recognizable amounts in vascular endothelium, in connective-tissue cells, on collagen fibres and in certain types of epithelium. But the greater part of the protein is removed from the circulating tissue fluids by phagocytosis in the cells of the reticulo-endothelial system, and it is the specific reaction of these cells to the alien antigen that is responsible for the development of hypersensitivity. For it is within the cytoplasm of these specialized cells that the globulins of the plasma are elaborated, and it is under the influence of the newly ingested antigenic protein that these globulins in the course of their formation acquire—perhaps the simile of mould and cast may be appropriate—the distinctive character of the particular specific antibody. Such an antibody is produced with notable ease when the provocative antigen is the protein of some foreign animal species but, whilst a little is produced and liberated into the tissue fluids after the lapse of a few days, the great bulk of it usually appears in the circulating blood some ten days after the inoculation has been made. It was this correspondence in time between the rapid rise in the anti-horse antibody titre of the children's sera and the onset of the clinical features of serum sickness that provided von Pirquet and Schick with one of their leading clues in their search for the pathogenesis of the condition.

Although the concept of the 'fixation' of antigens and antibodies to various types of cell has been powerfully supported in recent years by the findings with fluorescent microscopy, the idea was originally developed from analyses of the mechanism of anaphylaxis, and the support given to the ' cellular', as opposed to the 'humoral', school through the demonstration by Schultz and Dale that anaphylactic responses can be obtained with excised and perfused muscular structures such as the ileum and uterus of guinea-pigs. On these immunological foundations, the pathogenesis of serum sickness becomes comprehensible. The horse serum proteins—the provocative antigens—on entering the tissues by parenteral injection take two paths: the first leads to their fixation to various cells, especially of the vascular endothelium and connective tissues, in many parts of the body; the second takes them to the reticulo-endothelial cells where in the course of the following days they induce the formation of their specific antibodies. The flooding of the circulation with this liberated antibody some ten days after the therapeutic inoculation of diphtheria antitoxin leads to its wide-spread combination with the fixed antigens, the injury of the cells whose structure is so disturbed, and the local release of histamine and probably

of other pharmacologically active agents as well. It is this sudden release of histamine, acting on structures eminently sensitive to its presence, that results in the vascular disturbances that underlie urticaria and, in the case of asthma, to the contraction of the smooth muscle in the bronchi that is the cause of the respiratory obstruction.

HYPERSENSITIZATION BY FOREIGN PROTEINS

The analysis of the mechanism of serum sickness has been considered at some length because it was from the close study of this disease that much of our understanding of the pathogenesis of the hypersensitive state has been acquired. There are other routes than that of parenteral injection, however, by which foreign antigenic proteins can enter the body and bring about an allergic state initially and subsequently, on re-exposure, a clinical allergic response.

The respiratory tract has long been recognized as a peculiarly vulnerable structure, a susceptibility that it probably owes to its frequent exposure to protein-containing dusts and its inability to destroy them by secreted proteolytic enzymes. In former times, when the materials used in homes and factories were less numerous than they are today, most of the allergic respiratory disturbances were attributable to plant pollens, household dust and various animal danders. But in recent years, the number of potentially effective allergens has been much increased through the introduction of many new organic materials into commerce and industry. The dusts created by the working of certain tropical timbers now coming into use in this country for cabinet making have been found to excite an allergic asthma in some of the men who use them. Of longer recognition, though only comparatively recently shown to have an allergic pathogenesis, is the 'Monday fever' of the Lancashire cotton spinners which results from prolonged exposure to the protein-containing dust from the fibres.

Although much the greater part of the protein taken in food is broken down enzymatically before its absorption, there is now ample evidence that small quantities may penetrate the intestinal mucosa in an undenatured and immunologically active state. This absorption of intact protein takes place with notable ease in very young infants and, indeed, provides in many herbivorous animals the main route for the transference of maternal immunity from mother to offspring. But in adults also, especially should their alimentary tract be temporarily inflamed, small quantities of unchanged protein can pass through the mucosal epithelium. This penetration can be demonstrated very elegantly by a modification of the well-known Prausnitz-Küstner reaction that was devised by Walzer.

If a small amount of serum from a person who presents some variety of food allergy be injected intradermally into a *normal* person, and that person ingest within the next few days some of the peccant food, an urticarial reaction will shortly develop at the site of the skin injection.

This response depends upon the previous sensitization of the subject's skin cells through the local fixation of specific antibodies in the patient's

serum, and the later injury to these cells when they become exposed to trace amounts of the absorbed and circulating antigenic protein.

HYPERSENSITIZATION BY DRUGS AND CHEMICALS

Early in the present century, it was found that some forms of chemical treatment, such as exposure to nitric acid or to iodine, can so alter the configuration of a protein that it can become antigenic even within the animal from which it was originally obtained. For long, the significance of this work remained unappreciated, and it was only with the exploitation of this whole new field of 'artificial antigens' by Landsteiner and his colleagues that the real significance of such observations became recognized.

It is unnecessary here to describe in detail the pioneer researches made by this School; it will suffice to point out that these investigators were able to devise methods for the firm chemical coupling of certain comparatively simple substances to proteins and as a result to modify very materially their former immunological distinctiveness. For instance, if the arsenobenzene compound, arsanilic acid, were attached to a purified protein such as egg albumin, an antibody made against this new and artificial antigen would react immunologically by the classical precipitin test with the artificial antigen similarly created by coupling arsanilic acid to a horse serum protein. In short, the immunological specificity of the new complex no longer resided in the protein but in the chemical side chain, or 'haptene', which had been attached to it.

For long, observations of this kind, although of undisputed academic interest, appeared to have little bearing on the practical problems of allergy, because the methods employed for uniting the chemical haptene to the protein carrier required chemical reactions of a kind that could not take place in living tissues. Subsequently, however, when other types of union had been more fully explored, it was found that a sufficiently stable coupling could follow the exposure of a protein to certain chemicals under conditions so nearly physiological that combination between the two might confidently be expected to take place readily in a biological environment. Moreover, as with the earlier more rigorously chemical studies, it became apparent that even in these milder reactions enough haptene molecules could become attached in this way to confer new and distinctive immunological properties on the protein used.

There can now be little doubt that unions of this latter mild kind between proteins and haptenes in living tissues provide the basis for many of the allergic sensitizations to common drugs and chemicals that are now encountered with increasing frequency in clinical practice. Many of the sulphonamide drugs can be shown to combine readily with serum albumin, and this new artificial antigen, formed by the union of the drug and the protein in the circulating blood, is almost certainly responsible for the not uncommon occurrence of a serum sickness-like reaction after the administration of these chemotherapeutic substances. Similarly, there are strong indications that the absorption of 'sedormid' is followed in occasional patients by its coupling with blood platelets, and the resulting anti-'sedormid'-platelet antiserum so evoked is responsible for the profound thrombocytopenia and purpura that are sometimes met with after repetitions in the use of

this drug. Moreover, many of the forms of 'contact dermatitis', formerly seen in gardeners after handling primulas and now very common sequelæ of many industrial and domestic occupations, are similarly attributable to the attachment of the chemical to some cutaneous protein and the consequent autoimmunization of the patient to an artificial antigen created in his own dermis.

VARIATIONS IN THE RATES OF APPEARANCE OF HYPERSENSITIVITY REACTIONS

One of the features of hypersensitivity reactions which has proved notably perplexing is the wide variation in the latent period of their onset after exposure to the provocative agent, and the terms 'immediate', 'accelerated', and 'delayed' have come into use to distinguish the various clinical forms. Whilst the basic immunological and pharmacological understanding of these differences is far from complete, sufficient is now known for some general remarks on the subject to serve a useful purpose.

'IMMEDIATE' REACTIONS

The classical form of the immediate reaction, and the one which presents it in its most dramatic and feared form, is the anaphylactic death of hypersensitive persons and animals. In principle, such reactions differ in no essential respect from the immediate cutaneous reactions commonly obtained in clinical practice when precautionary intradermal inoculations of diluted serum are used before the administration of antitoxin. Their difference lies in the scale of the phenomena: the former is a generalized and the latter a localized reaction—an anaphylaxis in miniature.

The immunological basis for such immediate reactions is believed to rest upon some previous sensitization of the tissues generally, either by the particular protein itself or by one so nearly related that it shares many of its distinctive antigenic characters. The not uncommon severity of the reaction of children who have been brought up in close association with horses to first inoculations of antitoxin is an instance of such an allergic response in which long exposure by inhalation to small amounts of horse dander has sensitized the child to horse serum proteins as well. Once the specific antibodies have been formed and liberated by the reticuloendothelial cells, distributed in the circulating body fluids and widely fixed by many cells, the tissues become vulnerable to an antigen-antibody combination should the former be introduced parenterally on some subsequent occasion. An intradermal injection of the skin, for example, causes local injury, histamine release and a small hyperæmic weal; a general injection brings about a sudden injury to many cells almost simultaneously, and may occasionally—and notably in asthmatic subjects—result in death in anaphylaxis from acute histamine poisoning.

Although the sudden release of a large amount of histamine may be followed by serious disturbances in both the circulatory and respiratory systems, it should not be forgotten that the body possesses a potent

histamine-destroying enzyme in many of its tissues. This histaminase is capable of detoxicating histamine, but only within certain quantitative limits as can be shown by the following observation from animal toxicology.

The fatal dose of histamine for a rabbit, if injected intravenously and suddenly, is about 0.6 mg. per kg.; if injected by the same route, but slowly over a period of an hour, ten times as much can be given without the animal showing any distress.

The gravity of a hypersensitivity reaction of the immediate kind will thus depend, *inter alia*, upon both the amount and the rate of the resulting histamine release. A dose of antitoxin given to an allergic patient may kill him quickly with an anaphylactic shock if given intravenously and quickly, but be quite harmless if administered by a route entailing slower absorption and over a longer time. The quantity of histamine that is liberated may be the same by all methods of inoculation, but, like the rabbit, the patient can cope with the histamine if his detoxicating mechanism is allowed the necessary time to operate. In all hypersensitivity reactions of this immediate and potentially dangerous type, both quantity and time must be taken into consideration; it is this compromise which makes possible the progressive desensitization procedures that can be safely employed when larger doses of antitoxin are needed for therapeutic reasons.

Apart from such iatrogenic diseases as serum sickness, immediate reactions are liable to take place whenever the antigen is brought suddenly and intimately into contact with tissues that are both sensitized to it and susceptible to the action of the histamine that its presence may evoke. The inhalation of pollen or animal dander provides precisely this concurrence: the submucous tissues of the respiratory tract have become locally sensitized through previous exposure to such agents and the sudden re-exposure, leading to an antigen-antibody reaction in the mucosa and the liberation of histamine in close proximity to the bronchial musculature, leads to its prompt constriction and the consequent asthmatic attack. Probably the food allergies have a similar pathogenesis, the offending material, such as egg or fish protein, acting in such a way as to produce mucosal hyperæmia and exaggerated action of the intestinal musculature.

'ACCELERATED' REACTIONS

The 'accelerated' reactions are those in which the antigen brings about a response after some two or three days in a subject who, while not fully hypersensitive, has had some previous exposure to the material and whose antibody-forming cells respond in consequence more rapidly than usual. This type of reaction was familiar to von Pirquet and Schick from their study of serum sickness. But long before, as the following excerpt shows, it had been recognized by Jenner as an occasional sequel of vaccination.

'It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the Small Pox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable too, that whether this

change has been effected by the Small Pox, or the Cow Pox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter'.

'DELAYED' REACTIONS

The 'delayed' reactions have proved both more complex and more difficult of analysis, and it may be stated at once that they fall into two wholly different groups. Serum sickness may be taken as the type response of one; the tuberculin reaction can be regarded as most characteristic of the other. Since the pathogenesis of serum sickness has already been discussed, the following brief remarks will be confined to the tuberculin-type response.

Although in tuberculin reactions the local hyperæmia and weal do not follow the injection of the antigen for some twenty-four to forty-eight hours, there are reasons for believing that certain much earlier changes take place at the site which increase the permeability of the local cutaneous capillaries. This can be demonstrated in a tuberculous animal, for if the intradermal inoculation of the tuberculin is quickly followed by an intravenous injection of the colloidal dye, trypan blue, the local skin soon becomes coloured with the stain. If such reactive areas are examined histologically after various intervals, it can be seen that the lesion develops gradually: the small dermal blood vessels become increasingly dilated and large numbers of lymphocytes escape into the extravascular tissue spaces.

It is now believed that in tuberculosis and certain other allergic states recognizable through delayed reactions, little or none of the responsible antibody is free in the plasma—as in reactions of the immediate type—but that the great bulk of it is transported within the cytoplasm of the lymphocytes. The passive transfer of tuberculin sensitivity to a normal animal, almost or quite impossible with serum, can be effected readily with suspensions of lymphocytes obtained from infected animals. It would seem that the presence of these cells in the area is required before the pharmacological agents responsible for the hyperæmia and weal can be sufficiently released. The delay in the development of reactions such as that caused by tuberculin thus appears to depend upon a gradual build-up over a period of hours: the early and almost imperceptible vascular changes leading to the extravasation of a few specific antibody-bearing lymphocytes, followed by their reaction with the inoculated antigen—the whole inflammatory reaction gradually growing in intensity as more lymphocytes are brought to the site and the inoculated tuberculin, or other comparable antigen, is neutralized or removed along cutaneous lymphatic channels.

HYPERSENSITIVITY IN THE PATHOGENESIS OF CERTAIN DISEASES OF MAN

In several diseases of obscure etiology, there are grounds for the belief that an acquired hypersensitization to some antigenic agent may form an essential link in their pathogenesis. In some such instances, of which rheumatic fever and acute nephritis are conspicuous examples, their characteristic appearance after a local hæmolytic streptococcal infection occurs too often

for the association to be attributable to mere chance. Repeated failure to recover this coccus from cardiac, joint or renal lesions, however, together with the usual interval of some two weeks between the initial infection and the onset of clinical signs has long suggested the possibility—foreshadowed by Schick over forty years ago—that in these diseases the widely generalized manifestations may have an allergic pathogenesis.

What form the mechanism of such a hypothetical allergic reaction might assume in these circumstances is still largely speculative, although in recent years light has been shed on this question as a result of the creation of morphologically similar lesions in animals by experimental procedures calculated to induce hypersensitivity. If the supposition be well founded that acute nephritis in man is an allergic response to some streptococcal antigen, the lesion might arise in one or other of two ways. Either the specific bacterial antigen might be retained and concentrated within the substance of the glomerulus and there react later to the detriment of local structures with its antibody when the latter gains entry to the circulation some ten or so days later, or some immunological kinship may exist between a product of the bacterium and some component of the glomerulus which would lead after the same interval of time to the antibody evoked by the coccal antigen reacting with its analogue in the previous normal kidney. This latter possibility, though difficult to demonstrate, is not inconceivable for some instances are already known of heterophil antigens of the Forssman type that are common both to certain bacteria and to human cells.

The pneumococcus Type 14 possesses an antigen that is closely related immunologically to an antigen that is present in Group A red corpuscles—an observation which emerged from the clinical experience that the intravenous administration of Type 14 antipneumococcal horse serum therapeutically to pneumonia patients is sometimes followed by severe hæmoglobinuria and occasionally by death.

Some comparable kinship might similarly exist between an antigen in the hæmolytic streptococcus Type 12—the type that has been recovered with disproportionate frequency from the throats of patients suffering from acute nephritis—and some glomerular constituent of the human kidney. Were this so, the liberation of the specific antibody that follows infection with organisms of this type might lead to an allergic reaction in the kidney similar in character to those brought about by a nephrotoxic serum.

CONCLUSION

The many advances made by Coombs and others in the development of methods for the identification and estimation of antibodies of the so-called 'partial' or 'incomplete' varieties, which escape recognition in the earlier classical techniques of immunology, have provided a new and powerful weapon for a renewed attack on the pathogenesis of some of these putatively allergic diseases. As in the past, however, so clearly instanced in the study of von Pirquet and Schick, progress will depend upon close collaboration between laboratory workers engaged upon experimental immunological studies of a fundamental character and clinicians who are prepared to study and apply their findings to the analysis of these obscure syndromes.

HISTAMINE, THE ANTIHISTAMINES AND ALLERGY

By BERNARD N. HALPERN, M.D.

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ALLERGIC diseases are essentially functional disorders. These functional disorders, which are sometimes so dramatic that they may prove fatal, are conditioned by the release of biochemical substances initiated by the antigen-antibody reaction. Among these substances histamine is the most important —at least in man. Antihistamines are not only capable of antagonizing the effects of exogenous histamine, but also of providing protection against anaphylactic shock. The interest of the antihistamines for the clinician is correlated with the evidence of the part played by the release of histamine in allergic conditions. I therefore propose to review in the first place the role of histamine in allergy, and then to consider the general scope of the use of antihistamines in allergic diseases.

HISTAMINE AND ALLERGY

It was in 1910 that Dale and Laidlaw first postulated that histamine might be the hypothetical 'toxin' which Ch. Richet (1908) had invoked as the possible causative agent of anaphylactic shock. It is now known (Best, Dale, Dudley and Thorpe, 1927) that histamine is widely distributed in the various tissues of animals. Indeed, the amount of histamine in the body is of such magnitude that a total release would seriously endanger the life of the individual. Almost all the histamine is located in the cells where it is bound with some protoplasmic constituents in an inactive form (Gaddum, 1956). The distribution of histamine in the different tissues varies from one animal species to another. In general, large amounts of histamine are present in the skin, the lungs and gastro-intestinal tract. There is evidence that histamine can be released from the tissues by various specific and non-specific agents and stimuli. Histamine is probably involved in any inflammatory process (Halpern, 1953). The ingenious studies of Lewis (1927) fully established the conditions of release of a histamine-like substance by injury in the skin, which is responsible for the triple skin reaction.

The cumulating evidence of the last two decades has shown conclusively that histamine is responsible for anaphylactic shock, at least in certain animal species. The intravenous injection of an antigen into a sensitized dog is followed by a release of a considerable amount of histamine which can account for the clinical symptoms (Code, 1937). We have recently confirmed these observations.

Fig. 1 shows the correlation between the severity of the anaphylactic shock and the amount of released histamine in three dogs sensitized in the same manner. Dog

No. X reacted by an extremely severe shock and died about twenty minutes after the challenging injection: its plasma histamine level rose to 6000γ/1 (40γ/1 is normal); dog No. 43 responded by severe shock, as evidenced by the dramatic fall of

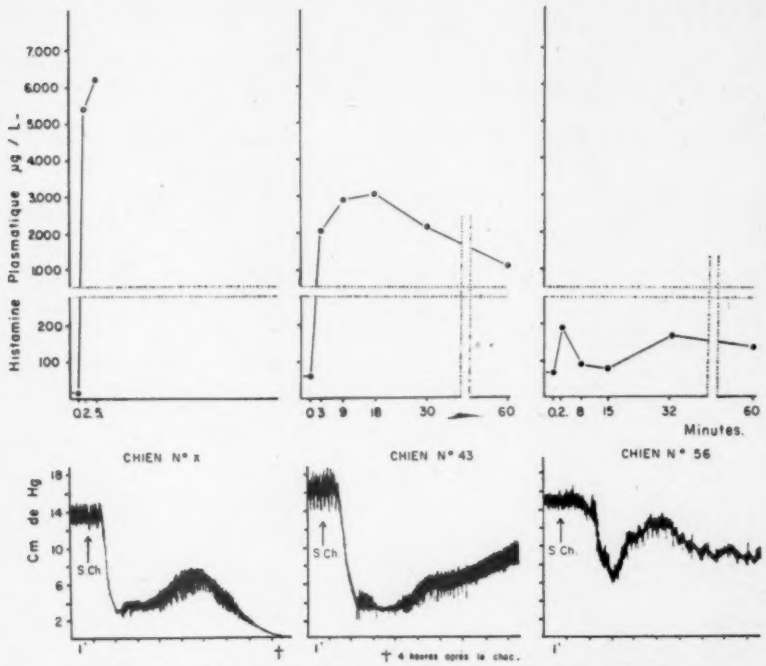


FIG. 1.—Anaphylactic shock in dogs sensitized to horse serum. Correlation between the gravity of shock and release of histamine. (S.Ch. = injection of horse serum.)

the blood pressure: its plasma histamine level went up to as much as 4000γ/1; it died four hours later; dog No. 56, which showed mild shock, had a moderate and transient increase of the plasma histamine level. Such a schematic correlation is not always obvious and should not be generalized to other animal species.

There is also definite evidence that the contact of sensitized tissues with the antigen causes a release of histamine (Bartosch, Feldberg and Nagel, 1932). This occurs not only with animals experimentally sensitized but also with human tissues removed from allergic patients. Schild *et al.* (1951) have shown in a convincing manner that isolated bronchi, surgically removed from a patient sensitized to pollen or to dust, are capable of releasing histamine 'in vitro' when the specific antigen is added to the fluid in which the tissue is immersed.

It is therefore beyond any doubt that histamine is released from the cells during the antigen-antibody reaction.

HISTAMINE LIBERATORS

Very similar to the antigen-antibody complex is the effect of a series of

substances recently described as histamine liberators, or histamine releasers. When injected into an animal or a man these substances are capable of producing curious clinical symptoms which, in many cases, are indistinguishable from specific allergic reactions. Some of these substances are of high molecular weight, e.g. dextran, ovomucoid, polyvinylpyrrolidone (Halpern, 1956), whilst others are chemically rather simple substances with a molecular weight in the range of alkaloids. A substance designated as 48/80 has been studied experimentally by Paton (1951), and by Feldberg and Talesnik (1953).

Another substance, which is a substituted butylamine, has recently been reported as having histamine-releasing properties (Charlier *et al.*, 1954; Feldberg and Lecomte, 1955; Halpern *et al.*, 1956). This substance, designated as 1935L, I have now used for more than eighteen months for clinical investigations in man. When injected into a non-allergic individual, a dose of 0.1 mg./kg. produces clinical symptoms which are identical with those produced by histamine: erythema, generalized pricking, headache, moderate fall of blood pressure and gastric hypersecretion (Lecomte, 1956). All these symptoms are easily controlled by an antihistamine. When injected into patients affected with allergic diseases, however, quite a different picture is elicited. After the first immediate symptoms, which are approximately similar to those in non-allergic subjects, a second phase of symptoms is observed during which the patient reproduces quite accurately his spontaneous clinical symptoms. Several of my patients affected with potential or actual urticaria have responded with a severe generalized urticaria but not with asthma. In asthmatic patients the same dose of the substance produces an asthmatic attack and, only very rarely, urticaria. The injection of this compound is followed by a considerable rise in the plasma histamine level.

Our investigations to date suggest that patterns of histamine release may differ in allergic and non-allergic patients. The interesting point is that individuals treated repeatedly by injections of this compound at adequate intervals of time, develop refractoriness to the histamine liberator, probably by depletion of available histamine. The establishment of the state of refractoriness is paralleled by a considerable clinical improvement in the spontaneous allergic symptoms and it is highly probable that there is a direct relation between the two factors. Furthermore, investigations performed with the histamine liberators have also disclosed that cortisone exerts an inhibitory action on the biogenesis of endogenous histamine (Halpern and Briot, 1955). The results obtained with the histamine liberators establish a sort of bridge between the effects of histamine itself and the antigen-antibody reactions. They also corroborate strongly the histamine theory of allergy.

I have already mentioned the report by Schild *et al.* (1951) that, when in contact with the respiratory allergen, histamine is released from the bronchi and lung tissues of patients sensitized to pollen and house dust. The figures

available on histamine release in clinical allergic diseases, however, are very incomplete and even contradictory (Rose and Browne, 1940; Capps and Young, 1940; De Gara, 1951). There are several possible explanations for this. Most of the investigators have measured the whole blood histamine content, which often reflects the white-cell fluctuations rather than the true plasma histamine. Furthermore, in most clinical allergic conditions the release of histamine is progressive and may not produce blood histamine changes detectable by our techniques; when histamine is released, it is permanently destroyed by tissue histaminase and is also eliminated rapidly through the kidneys. Unless these factors are controlled, no credence can be attached to the blood histamine estimations. In a few cases, in which some of the necessary precautions have been taken, a significant increase of histamine has been found (Henderson, Code and Roth, 1957). Much work still remains to be done on the problem of histamine release in clinical allergy.

ANTIHISTAMINES AND ALLERGY

It was the demonstration of the anti-anaphylactic properties of the antihistamines that led to their use in clinical allergy (Bovet and Staub, 1937; Halpern, 1942). This is one of the few examples in therapeutics where the use of a drug has been based only on pharmacological data. I still recall very vividly those early days when the first positive clinical results with the antihistamines were reported. It seemed unbelievable! Today, the wheel has gone full circle and we are now perplexed by some incomplete results or unexplained failures! The clinical reception of the antihistamines was so enthusiastic that thousands of compounds have been synthetized; only thirty of them (too many in my opinion) have been introduced for clinical use. Although the antihistamines vary widely in their chemical structure, most of them have a common chemical basis which can be represented by the following structural formula:

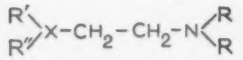
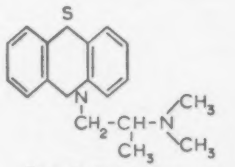


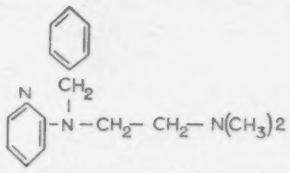
Figure 2 shows the chemical formulæ of some of the more widely used antihistamines.

Somewhat different in chemical structure are the phenothiazine derivatives, among which promethazine is the most outstanding representative:—

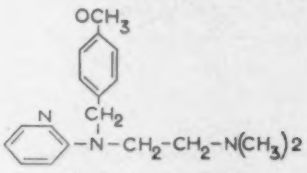


Promethazine ('phenergan')

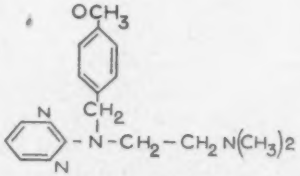
Despite the chemical differences there are but slight variations in the therapeutic efficacy of most of the antihistamines. Special reference must be made to promethazine, which is still the most potent antihistaminic and one



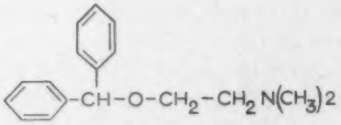
Tripelennamine ('pyribenzamine')



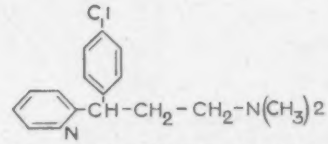
Mepyramine 'anthisan')



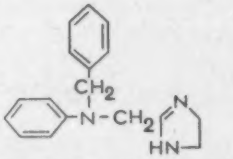
Thonzylamine ('neohetramine')



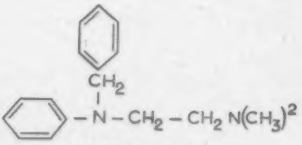
Diphenhydramine ('benadryl'



Chlorpheniramine ('chlor-trimeton'; 'piriton'



Antazoline ('antistin'; 'histostab')



'Antergan'

FIG. 2.—Chemical formulæ of some of the more widely used antihistamines.

which possesses potent sedative effects. It was a study of these sedative properties of promethazine which led to the discovery of chlorpromazine, of which promethazine is the direct precursor.

The antihistamine drugs are capable of antagonizing, to a varying degree, many, but not all, of the effects of histamine. They neutralize very efficaciously the stimulatory action of histamine on smooth muscle; their action on the vasodepressor effects of histamine is less evident whilst the gastric secretagogue action of histamine remains unaffected. One of the most striking properties of the antihistamines is their ability to reduce the capillary permeability entrained by histamine and allergic procedures (Halpern, 1949). This essential property provides the basic mechanism by which the antihistamines affect the allergic process.

The intimate mechanism of action of the antihistamines is still unknown. It is generally accepted that these substances behave as blocking agents as they are competing with histamine for the same receptors: it is presumed that the antihistaminics occupy the specific receptors on which histamine is usually fixed. When quantitatively compared it became obvious at an early stage that antihistaminic substances were much more effective in protecting animals from histamine than from anaphylactic reactions. This is true not only for animals 'in toto' but also for isolated organs. It is very unlikely that these differences are referable to the release of some other hypothetical mediators different from histamine, and it is generally assumed that the blocking agent is more efficient against histamine which gains access to an effector cell by way of the circulation than that which is released intracellularly by the reaction between antigen and antibody (Dale, 1948). A similar phenomenon occurs with other autonomic blocking agents which, at some sites, antagonize the effects of circulating neuro-humoral transmitters more effectively than the effects of nerve impulses. This may provide a partial explanation of some of the inconstancies of antihistaminic therapy (Goodman and Gillman, 1956).

THERAPEUTIC USES OF THE ANTIHISTAMINES

The antihistaminic substances now form a definite pharmacological group of therapeutic agents exhibiting valuable palliative action on symptoms of a variety of allergic diseases. The efficacy of these drugs, however, is very unequal and capricious and, whilst they produce definite improvements in certain affections, they appear to be without action on others—for still unexplained reasons.

Acute anaphylactic shock.—The injection of heterologous sera, of drugs such as penicillin, and of specific antigens, as well as bites by certain insects may cause a severe anaphylactic-like shock with acute vascular collapse, which may sometimes be fatal. In such cases, antihistamines are really life-saving. In these cases, the preparation should be given parenterally, and concurrently with adrenaline, so as to control the vascular collapse as rapidly as possible.

Serum sickness.—Antihistamines are generally very valuable for relief of the symptoms of serum sickness, whether these symptoms are caused by therapeutic sera or by certain drugs (penicillin). The pruritus is rapidly controlled and the eruption subsides usually in a few hours. At the present time, it is certainly the only efficient treatment for this affection. Some individuals respond better to one type of drug whilst others will do better with another one. Treatment should be maintained for several days if a recurrence of symptoms is to be avoided.

Dermatoses.—Antihistamines are the treatment of choice in acute urticaria and many forms of angioneurotic œdema. The results are often spectacular and successes have been claimed in about 80 per cent. of patients (Arbesman, 1947). In chronic urticaria the results are less favourable but certain symptoms, such as itching, are relieved in a high percentage of cases. In atopic dermatitis the antihistamines provide a sedation for itching. As a result, scratching is discontinued and the lesions improve by avoidance of mechanical irritation and secondary infections.

Local applications of ointments and creams are widely used for this group of diseases but a warning must be given against their abuse: prolonged topical applications of these drugs may result in skin sensitization.

Hay fever.—In general, patients with seasonal hay fever respond in a gratifying manner to antihistaminic therapy. Different workers report 60 to 80 per cent of patients obtaining relief, although this is seldom complete. The relief consists usually in cessation of sneezing, in drying of the mucous membrane and in disappearance of the conjunctival pruritus. Very often an unpleasant feeling of nasal blocking persists. The efficacy of the antihistamines depends upon the severity of the symptoms: patients with grass hay fever respond much better to antihistaminic therapy than patients sensitized to ragweed pollen.

In perennial vasomotor rhinitis the results are much more irregular and acute symptoms are controlled more readily than persistent nasal congestion. In both groups of diseases, allergic specific hyposensitization is the treatment of choice.

Asthma.—Antihistamines produce definite improvement in certain cases of asthma; in others they are very disappointing. A few years ago, we (Pasteur Vallery-Radot, Halpern and Blamoutier, 1948) showed that promethazine when given prophylactically is able to protect regularly an allergic subject against asthma produced by certain animal proteins such as danders, feathers, horse serum and fish glue, whilst the same treatment was ineffective in infective asthma or even in asthma caused by dust or pollen. The reason for this difference in action is not clear. Bronchoscopic studies have shown that in the first group of patients the main cause of the dyspnœa was an intense œdema of the bronchi, which was much less evident in the second group. The causes of dyspnœa in asthma differ with the various forms of asthma: œdema, spasm, bronchial congestion, secretory disorders, vegetative nervous imbalance. It is probable that the antihistamines do not affect

these different disorders to the same degree. It appeared to us that antihistamines were particularly effective in cases of asthma due to high molecular weight proteins and in which œdema was the dominant symptom.

The common cold.—The problem of the action of antihistamines in the common cold has been much debated and contested. In fact, several groups of investigators concluded on the basis of statistical analyses performed on homogeneous populations that, if antihistaminic therapy was initiated at the early stage of a common cold, the disease could be aborted. If therapy was started later, some symptomatic relief would be afforded and the evolution of the common cold would be shortened. Other carefully controlled studies failed to support these conclusions. In a condition such as the common cold, where the spontaneous evolution of the affection is very capricious and unpredictable and for which no objective valid criteria are really available, statistical estimations are of doubtful help. My feeling, based on personal experience, is that antihistamines relieve the symptoms of the common cold. This is probably attributable to the fact that the main property of the antihistamines is an inhibitory effect on capillary permeability (Halpern, 1949), whatever the immediate cause may be. Consequently they reduce œdema of the mucosa, rhinorrhœa and nasal congestion. Their action is particularly beneficial in persons with perennial or seasonal allergic rhinitis with a superimposed cold. The shortening of the common cold may result from the fact that the resistance of dried mucosa is greater to local infections (Sherman, 1951).

Miscellaneous conditions.—Beneficial results with antihistamines have been reported in many other conditions for which an allergic origin is far from being proved: e.g. pruritus ani and vulvæ, Ménière's syndrome, herpes zoster, whilst certain antihistamines are very effective in controlling symptoms of motion sickness.

SIDE-EFFECTS

Organotropic toxicity of these substances is very low. The incidence of severe accidents is small compared with the enormous consumption of these drugs. Only a few cases of agranulocytosis have been reported. The most frequent reaction, and the one common to all antihistamines, is sedation. This property is more pronounced with diphenhydramine and the phenothiazine derivatives than with other compounds. Decrease of dosage or the substitution of another antihistaminic may circumvent these untoward effects. Miscellaneous individual side-effects, such as pyrosis, nausea, dizziness, somnolence or nervousness, and tremors, have been reported.

SUMMARY

Allergic diseases are an important social and economic problem as a great number of individuals are affected in all countries of the world. In the present state of knowledge, it is impossible to influence the genetically acquired tendency of certain persons to become sensitized to common

surrounding substances. Much more successful have been the attempts to combat the effects of the mediators released by the antigen-antibody reaction, among which histamine is the most important agent. The interest raised by the antihistamines is only partially attributable to their therapeutic action; their discovery contributed new tools for the study of the role of histamine in many physiological and pathological processes.

The effects produced by the histamine liberators, the evidence provided that cortisone acts on allergic conditions by inhibiting the biogenesis of endogenous histamine, the protective action of the specific histamine antagonists against anaphylaxis, and their therapeutic effects in typical allergic diseases are all prevalent evidence of the dominant role of histamine in allergic states, and justify the hope that more progress will soon be achieved in the treatment of allergic diseases by controlling the metabolism and the effects of histamine.

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RHEUMATIC FEVER AND ALLERGY

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INFECTION with hæmolytic streptococci induces rheumatic fever in susceptible people. In this article, the various ways in which these organisms can damage tissues are considered. By a process of exclusion, combined with direct evidence, the hypothesis is advanced that, in rheumatic fever, damage is due to streptococcal allergens.

Prevention, or prompt treatment, of streptococcal tonsillitis will hinder the appearance of the rheumatic syndrome, but once the symptoms of the latter appear such therapy is ineffective (Rantz, *et al.*, 1945). With the possible exception of cortisone therapy, no method of artificially decreasing susceptibility has been found. Reinfection with streptococci produces a recurrence only in about half the patients involved (Coburn and Moore, 1942). Therefore, susceptibility must be a variable factor and the possibility of influencing it must exist. The hypothesis that susceptibility to rheumatic fever and sensitivity to bacterial allergens are analogous conditions has led me to study in experimental animals the influence of certain nutritional and hormonal factors upon sensitivity to bacterial allergens. The nutritional and hormonal factors were selected for study because there was clinical evidence to suggest that they might play significant roles in influencing susceptibility to rheumatic fever (Long, 1954). For the sake of brevity, the many current alternative hypotheses on the pathogenesis of rheumatic fever will only be mentioned briefly, but references to more detailed criticism will be provided.

THE HÆMOLYTIC STREPTOCOCCI

Hæmolytic streptococci can damage the body in two main ways: directly by invading the tissues and producing a pyogenic cellulitis, or indirectly by diffusion of exotoxins or allergens from infected to non-infected tissue.

Rheumatic lesions are non-pyogenic and bacteria-free. They do not resemble the lesions produced by exotoxins in general or streptococcal exotoxins in particular. On the other hand, they are compatible with an allergic reaction. They show extensive œdema, increased capillary permeability, fibrinoid necrosis, accumulation of mononuclear cells and absence of polymorphonuclear cells. Klinge (1929, 1933) considered that in a systemic disease the presence of such changes was presumptive evidence of a hypersensitivity reaction. Certainly, systemic diseases of this type have not been shown to occur in the absence of naturally occurring or artificially induced allergic reactions. Rheumatic fever is not due to a simple toxæmia. Indeed, the severity of the streptococcal infection and the incidence of rheumatic fever show no correlation. Moreover, there is no failure of immunity to streptococcal antigens; in fact the level of circulating antibody is abnormally

high in these patients. The level of fixed antibody, judged by hypersensitivity to streptococcal allergens, is also high (Coburn, 1931; Swift *et al.*, 1928). The type of allergic response is that typified by the tuberculin reaction (Swift *et al.*, 1928). It may be significant that in the guinea-pig, cells damaged by a specific streptococcal toxin are more susceptible to bacterial allergens than cells not so damaged and this may in part explain the particular role of the streptococcus (Grey and Long, 1954).

Further, the susceptibility of the few, and the liability of those few to recurrence of rheumatic fever, suggest that bacterial allergens are more important than bacterial toxins in the pathogenesis of the disease. There are non-specific ways in which hæmolytic streptococci can harm the host (Long, 1956a). The best known 'non-specific' hypothesis is that rheumatic fever is due to 'stress'; that hæmolytic streptococci are 'non-specific provocatives' (Waksman, 1949). This hypothesis has been criticised in detail elsewhere (Long, 1954). But even if the concept of 'stress' and the adaptation syndrome is incompatible with clinical experience, bacterial infection undoubtedly leads to a change in the ratio of activity of the endocrine glands.

CHANGES IN ENDOCRINE BALANCE

During the early acute stages of a bacterial infection, adrenocortical stimulation, increased excretion of urinary corticosteroids, increased excretion of nitrogen, and mobilization of glucose are related phenomena. This catabolic phase of infection ends with the development of immunity and, as a result, convalescence begins. The anabolic phase of convalescence is associated with depressed adrenocortical formation and increased insulin secretion. Rheumatic fever occurs approximately three weeks after the streptococcal infection as a complication of convalescence and presumably therefore during the anabolic phase.

The changes in endocrine balance, associated in the early stages of infection with catabolism and in the later stages with anabolism, have been shown in the guinea-pig to influence profoundly the level of circulating antitoxin and the degree of sensitivity to bacterial allergens (Long, 1956a). If the analogy between animal and man holds, the post-streptococcal state of Rantz will be associated with a relative increase in insulin secretion resulting in hyperimmunity (Long and Shewell, 1955) and hypersensitivity (Long and Shewell, 1954) to streptococcal antigens. If this hypothesis is correct, rheumatic fever may be initiated by hypersensitivity to streptococcal allergens made worse by the hyperinsulinism essential to convalescence. On this basis, cortisone therapy prolongs the acute stage of adrenocortical stimulation associated with decreased sensitivity to bacterial allergens and delays a too early convalescence associated with an excess of insulin and increased sensitivity to bacterial allergens. This hypothesis is compatible with the facts (Long, 1954, 1956a). (It is important to appreciate that cortisone therapy, unlike insulin therapy in diabetes mellitus, does not consist in replacement of a deficient hormone but the artificial production of an un-

natural state of hyperadrenalism. It is pharmacological, not physiological, therapy.)

THE ALLERGIC HYPOTHESIS

The allergic hypothesis is based upon the exclusion of other types of bacterial damage, together with direct evidence that hypersensitivity to streptococcal allergens occurs in rheumatic patients. The fact that hypersensitivity to these allergens complicates what Rantz and his colleagues (1946) have called the 'post-streptococcal state' without necessarily inducing rheumatic fever, is not incompatible with the allergic hypothesis. Clearly, the degree of sensitivity to streptococcal allergens and the susceptibility of the host may decide the incidence and severity of the rheumatic syndrome. But the fact that low sensitivity to streptococcal allergens may occur in a resistant host without resulting in rheumatic fever, does not invalidate the allergic hypothesis. If this concept is correct, we might expect all grades of rheumatic fever ranging from subclinical to the full syndrome. This in fact occurs. The symptoms of the disease may be so mild that the end-result of rheumatic carditis, a valvular lesion, is often found in patients without a history of rheumatic fever. Indeed, the 'post-streptococcal state of Rantz' may perhaps be defined as a phase of convalescence from streptococcal infection in which one or more symptoms of rheumatic fever occur without the diagnosis of rheumatic fever being made (Long, 1956a).

The analogy between the response of man to tuberculous infection on the one hand, and to streptococcal infection on the other hand, also supports the allergic hypothesis. Although every student knows that primary infection with tubercle bacilli leads to a severe local reaction at the site of re-infection—the Koch phenomenon—it is seldom appreciated that in infants an analogous response occurs to streptococcal infection. Initial infections are diffuse and difficult to diagnose, repeated reinfection is associated with an intense localized response; this reaches maximum severity in the age-group with the highest incidence of rheumatic fever (Powers and Boisvert, 1944; Paul and Salinger, 1931); at this stage reinfection occurs in hyperimmune, hypersensitive children.

The therapeutic effect of cortisone is usually attributed to its 'anti-phlogistic' action. The use of this meaningless term has been criticized elsewhere (Long, 1954). In the species most analogous to man, the guinea-pig, cortisone has no effect on the progress of infection with hæmolytic streptococci. It has no effect on the lesions caused by injection of streptococcal filtrates containing all the soluble products and exotoxins produced by this organism. It depresses sensitivity to streptococcal allergens. Indeed it is probable that in species like man, cortisone depresses sensitivity to bacterial allergens and has no other significant action on inflammation of bacterial origin (Long, 1954). Even then the quantity of fixed antibody—that is to say the basic allergic state—is not depressed; in the guinea-pig at least, cortisone merely diminishes the amount of damage caused by union of fixed antibody and bacterial allergen (Long, 1954). It cannot be too

strongly emphasized that there is clear-cut species difference in immunological behaviour, in response to stress, in resistance to cortisone (Shewell and Long, 1956) and in metabolism of ascorbic acid (Long, 1954, 1956a, 1957); and, moreover, that these are closely interrelated (Long, 1956a). The only significant anti-inflammatory action that cortisone exerts in species analogous to man is anti-allergic activity (Long, 1954). If, then, cortisone relieves the symptoms of rheumatic fever by opposing the hæmolytic streptococcus, it almost certainly opposes damage due to streptococcal allergens. The alternative hypothesis is that cortisone produces its therapeutic effect in some way other than as an anti-inflammatory agent (Long, 1955).

It is not the purpose of this article to consider the various modifications and alternative allergic hypotheses. The distinctions between immediate and delayed allergic responses and between the anaphylactic, iso-sensitization and auto-sensitization hypotheses have been considered elsewhere (Long, 1956b). None, in my opinion, merits consideration until the hypothesis of bacterial allergy has been disproved. Neither is it intended to consider the clues to the pathogenesis of rheumatic fever provided by a study of the collagen diseases as a whole. The assumption will be made that hypersensitivity, of the tuberculin type, to streptococcal allergens produces rheumatic fever in susceptible people.

SUSCEPTIBILITY

This hypothesis, if true, has important implications. Undoubtedly, prophylactic treatment of streptococcal infection will prevent disease, but the possibility also exists of decreasing susceptibility to rheumatic fever. Susceptibility varies not only between nations, communities and income groups, but between individuals and in the same individual from time to time (Waksman, 1949). This would suggest that, although heredity, which cannot be readily controlled, apparently plays a role (Wilson and Schweitzer, 1937) it is a minor one. Hormonal and nutritional factors are probably of greater importance (Long, 1954). The facts that cortisone relieves the symptoms of the disease, and that the incidence is negligible in diabetes, show that endocrine balance is important. The remarkably low incidence in dairy-farming communities has been noted for half a century. That rheumatic fever is less common in the dairy-farming States than in the cotton and tobacco States in America (Peete, 1944) suggests that biologically valuable protein, or some related nutritional factor, may influence susceptibility to the disease. Wallis (1954) found that children who developed rheumatic fever gave a history of eating fewer eggs than children who did not develop the disease. Powdered egg yolk prevented recurrence of rheumatic fever in underprivileged children in spite of recurrent attacks of hæmolytic streptococcal infection (Coburn and Moore, 1942).

In my opinion, the most probable explanation of these facts is that the anti-rheumatic property of egg-yolk is due to its content of biologically valuable protein (Long, 1954, 1956a). This possibility could of course be

investigated by direct experiment. On the other hand, Coburn and his colleagues (1954) demonstrated an anti-allergic substance in egg-yolk to which might be attributed the anti-rheumatic activity of egg. Long and Martin (1956) found a similar, if not identical, substance to be present in small quantities in arachis oil and in large quantities in egg-yolk. The active substance appears to be an amine with about 10 to 14 carbon atoms. There would appear to be sufficient grounds to justify clinical trials to confirm or refute the anti-rheumatic property of egg-yolk. If such activity does exist, the role of protein or non-protein in producing this effect could readily be determined.

Although the number of substances that have anti-allergic activity is embarrassingly large (Long and Martin, 1956), and sensitivity to tuberculin (bacterial allergy) is a complex phenomenon which can be influenced by various factors (Long and Martin, 1956), these factors can be divided into two main groups: those, like cortisone, whose action is influenced by a diet deficient in ascorbic acid or by injection with reduced glutathione; and those, unlike cortisone, whose desensitizing action is independent of these factors. The possible modes of action of several of these substances, including cortisone, have been discussed elsewhere (Long, 1955).

CONCLUSION

It is my personal hope, maybe not a very substantial one, that a substance with the anti-allergic activity of cortisone, but without its side-effects, will eventually result from these studies. Whether or not this practical result is ever achieved, any experimental work that elucidates the therapeutic action of cortisone is relevant to 'rheumatic fever and allergy'.

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ALLERGIC REACTIONS TO DRUGS

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As therapy with chemically defined compounds continues to displace biological preparations, it might be anticipated that allergic reactions would become less of a problem for the physician. No such trend is evident. Certain newly synthesized drugs possess a startling capacity to produce completely unexpected effects, apparently allergic (hydrallazine, for example). Furthermore, as a rule a patient who sees a physician receives, in addition to physical examination and reassurance, one to half-a-dozen drugs designed to soothe him, pep him up, alter his mood, protect him from the onslaught of predatory micro-organisms or bring his blood pressure up or down. The patient is usually left in the dark as to the identity of the drugs given him and, for this reason, no advantage is taken of a capacity with which man above all living things is endowed, namely, memory for specific events. This attribute is not unlike allergy itself, differing chiefly perhaps in that an antigen-antibody reaction mediates the latter.

THE PROBLEM

The familiar and reasonable assumption that drugs combine with proteins in plasma and cells to form complete antigens continues to be reinforced rather than weakened by workers in the field of experimental immunology and allergy, but there seems to be no satisfactory explanation for the occurrence of allergy in certain patients and not in others. Allergic reactions seem to be, and perhaps actually are, more frequent among patients with asthma, hay fever and atopic dermatitis, but this commonly held view does not seem to have been put to a proper test. It is certainly true that a great many instances of drug allergy occur in persons who seem to lack the 'allergic diathesis'. On the other hand, it would appear that, whatever the incidence, the *intensity* of drug reactions is greater amongst 'allergic individuals'. Such persons are particularly prone to develop asthma, urticaria and collapse.

Factors which apparently predispose to allergic reactions to drugs are repeated exposure, topical application, especially to the skin and especially if the skin is already the site of an inflammatory reaction, and the parenteral administration of drugs combined with a menstruum or in a form designed to delay absorption. Borrowing from the experience in animals with adjuvants, which not only serve to delay absorption but which also, because of the incorporation of killed mycobacteria, induce a persisting inflammatory response at the injected site, it might be anticipated that the inadvertent injection of therapeutic agents into a site at which tissue had been injured by trauma, by impaired blood supply, by infection or by previous injections

would meet at least some of the conditions favouring the production of antibody to the drug injected.

Such considerations suggest that not all the factors concerned in the development of allergic reactions to drugs are beyond the control of the physician. He might do well therefore to avoid long-acting preparations, to give drugs by mouth whenever possible rather than by injection, to give as few drugs as possible, compatible with effective therapy, and to avoid using drugs topically which are useful when absorbed systemically. The physician is under pressure, however, to do otherwise. Drugs are marketed increasingly as mixtures in a single tablet, capsule, ointment or cream, under a trade name which may provide only a hint as to the contents. The patient, eager to try the latest in therapy, will be unaware that he has received one or more of the components before and indeed the physician himself may well have difficulty keeping track of what each new preparation contains. Injection often seems preferable because it is a more dramatic event for the patient

(A) Allergic	(B) Probably allergic	(C) Possibly or doubtfully allergic
1. Rash, usually maculopapular but variable and often associated with fever 2. Urticaria and angioneurotic edema 3. 'Serum disease' syndrome 4. Exfoliative dermatitis 5. Eosinophilia 6. Acute allergic or 'anaphylactic' shock, asthma, and urticaria, in combination or singly	1. Fever alone 2. Purpura (often not thrombocytopenic) 3. Granulocytopenia 4. Necrotizing angiitis (including polyarteritis) 5. Syndrome simulating disseminated lupus erythematosus	1. Leucopenia 2. Anæmia 3. Nephritis or nephrosis 4. Hepatitis 5. Aplastic anæmia 6. Acute hemolytic anæmia 7. Peripheral neuritis 8. Fibrinous pneumonia

TABLE I.—List of allergic or possibly allergic reactions to drugs.

than instructions to take 'one after each meal with a little water', and the doctor will have the comforting feeling that the medication is really *in*. Nevertheless, complex concoctions, an aura of mystery and the hypodermic syringe deserve decreasing prominence in modern drug therapy.

There is little reason to question the assumption that a period of five to ten days or more is required for allergy to a drug to develop following first exposure. Instances wherein an allergic reaction allegedly appeared promptly on first exposure may be explained in one of three ways: (1) previous contact with the drug in question had indeed occurred without the patient's or the physician's knowledge; (2) exposure in the past to a drug or drugs immunologically similar and chemically related to the drug in question; (3) misunderstanding as to the nature of the reaction which may have been toxic or idiosyncratic rather than allergic. The first two possibilities readily arise because therapeutic preparations often consist of two or more drugs in combination, marketed under a single trade name, or because significant exposure to antibacterial drugs, fungicides and insecticides has occurred through the use of these agents in animal husbandry and food growing.

In those who become allergic while receiving a drug, reactions such as rashes and fever usually appear in five to ten days, whereas granulocytopenia and aplastic anæmia, for example, rarely appear before treatment has been in progress for weeks or months. In those who are already allergic, however, reactions may develop very promptly. Acute allergic shock, urticaria, and asthma, singly or in combination, may follow a single dose of a drug within minutes, and fever, rashes, granulocytopenia and thrombocytopenia may develop within a few hours. The reactions tend to be severe, and continued administration of the offending drug in the face of such reactions is unquestionably hazardous.

DIAGNOSIS

Recognition of allergic reactions to drugs is based almost entirely upon the history and upon the nature of the reaction. A list of allergic or possibly allergic reactions is given in tables I, II and III. Drugs differ widely in their tendency to produce allergic reactions and, since the nature of the reaction will often depend upon the drug involved, careful identification of all drugs which the patient is currently taking is essential. A detailed history of past reactions to drugs should also be obtained, not omitting reactions to drugs which had been applied topically. Skin tests by the 'scratch' method or by intracutaneous injection, as done for diagnostic purposes in pollenosis, have no application in allergic reactions to drugs. To be sure, reactions are often obtainable by this means with penicillin and occasionally with other drugs, but their interpretation is so difficult as to render them virtually valueless. Many patients who develop a systemic allergic reaction to certain drugs given by mouth or by injection, will also react to the drug by patch test and this is likewise the rule among those who have acquired their allergy as a result of application of a drug to the skin. As such tests require the elapse of twenty-four to forty-eight hours before they can be read, however, and as severe systemic allergic reactions may follow such tests in highly allergic individuals their practicability and safety are open to question. One is dependent therefore on the history and on the nature of the reaction in order to establish the diagnosis.

Tables II and III attempt to indicate the nature and incidence of allergic reactions to some commonly used drugs. The incidence of reactions is difficult to determine. Those which arouse interest because they threaten life (granulocytopenia, for example) or seem bizarre (a syndrome simulating collagen disease) tend to be reported whereas minor reactions, such as rashes and fever, may only be described when they occur in the course of a systematic study of a particular drug. Thus, it may well be that the severer and more dangerous reactions appear to occur relatively more often than is actually the case. Further, the apparent capacity of a drug to cause allergic reactions may be influenced by the type of patient who receives them. The antihistamine drugs, for example, are most often used in patients who tend to have urticaria, allergic rhinitis or asthma. Such manifestations have been described as reactions to an antihistamine drug itself, but the drug's

role here is difficult to assess. A case in point is the reported occurrence of asthma as an allergic reaction to diphenhydramine. Manifestations of a serious illness (e.g. sepsis) may overshadow an allergic reaction to a drug, making the reaction difficult or impossible to recognize, or an allergic reac-

Name of drug	Relative tendency to produce reactions	The more common reactions*	The less common reactions*	Remarks
Sulphonamides	Moderate	A_1,B_1	$A_2,A_4,B_2,B_3,C_1,C_2,C_3$	Sulphathiazole and those drugs hydrolysed to sulphathiazole cause rashes more commonly than the others of this group, especially a type simulating erythema nodosum. Topical application can induce high degrees of allergy and is not advisable. The drugs of this group cross-react in some degree allergically. Sulphafurazole seems to produce fewest allergic reactions, but this drug is one of the more recently introduced sulphonamides.
Penicillin	High	A_1,A_2,A_3,B_1	A_4,B_4	Probably now causing more allergic reactions than the other anti-infectious agents combined, perhaps because of very wide use. The various penicillins tend to cross-react in allergic persons. Fever, malaise and lymphadenopathy occurring during treatment of primary or secondary syphilis ('Herxheimer's reaction') is not an allergic reaction to penicillin. The incidence of allergic reactions with various preparations is least with penicillin given by mouth, greater with crystalline penicillin given by injection, and greater still with procaine penicillin given by injection. The procaine present in the last is rarely a cause of difficulty.
Chlortetracycline, oxytetracycline and tetracycline	Moderate	A_1,B_1	——	Closely related chemically, they probably cross-react in allergic patients. The chief side-effects, mainly gastrointestinal (including pseudomembranous colitis), are probably not allergic.
Chloramphenicol	Low	A_1,B_1	C_3	Incidence of reactions is low, but because of the occasional occurrence of aplastic anæmia, which may be fatal, there is a tendency to use this drug less than the other antibiotics.
Streptomycin	High	A_1,A_2,B_1	A_3	This drug, often used for the treatment of tuberculosis, is given for long periods of time and this may explain the relatively high incidence of allergic reactions which are usually not serious. Deafness and labyrinthine involvement are not considered here. A histamine-like substance was present in early lots, causing flushing and a fall in blood pressure (Keefer and Hewitt, 1948).
Erythromycin	Very low	A_1	——	

TABLE II.—Type and approximate frequency of allergic or possibly allergic responses to sulphonamides and antibiotics.

*The letters and subscripts refer to the reactions listed under A, B and C in Table I.

tion might be suppressed during a severe infection, perhaps as a consequence of 'non-specific' tissue unresponsiveness or adrenocortical stimulation.

Certain drugs, some of which are not included in table I, produce striking, or exceptionally dangerous reactions. The tendency of aminopyrine to cause granulocytopenia is well known. Quinidine, quinine and 'sedormid' (allyl-isopropyl-acetyl-carbamide) have acquired a reputation for producing thrombocytopenic purpura. This has been studied in some detail (Acroid,

Name of drug	Relative tendency to produce reactions	The more common reactions*	The less common reactions*	Remarks
CARDIOVASCULAR DRUGS				
Digitalis	Extremely low	A_1	—	
Acetazolamide	Probably similar to other sulphonamide drugs			
Mercurials	Very low	A_2,A_4,B_1	A_1,B_4	Preparations for parenteral use are best not given intravenously.
Rauwolfia serpentina	Extremely low or absent	—	—	
Hydrallazine	Moderate	A_1,A_2,B_1	B_4,B_5	May produce a syndrome simulating collagen disease with many of the features of disseminated lupus erythematosus (see text).
Hexamethonium	Very low	A_1	C_2	May produce a respiratory syndrome characterized by dyspnœa and fibrinous pneumonia probably not allergic in nature (Doniach *et al.*, 1954; Perry *et al.*, 1957).
Veratrum	Extremely low or absent	—	—	
SEDATIVES				
Barbiturates	Moderate	A_1,B_1	A_4	Phenobarbitone is much more likely to produce allergic reactions than the other barbiturates.
Meperidine	Very low	A_2	—	
Morphine and opium derivatives	Very low	A_1	—	Mostly contact dermatitis among those who handle opium or its derivatives. Codeine may cause skin eruptions but these are very rare.
Chloral hydrate	Very low	A_1	—	
TRANQUILLIZERS				
Chlorpromazine and meprobamate	Low	A_1	B_1,B_2	Jaundice caused by chlorpromazine is probably not allergic in nature. Although reports of allergic, or presumably allergic, reactions keep appearing, the incidence of such reactions is probably low as these drugs have been very widely used.
ANTIHISTAMINICS				
	Very low	A_1	B_2	Scattered instances of urticaria and asthma have been reported, the significance of which is difficult to assess because, as a group, patients receiving the antihistaminic drugs tend to have such manifestations for a variety of causes. Tripelennamine chloride has been most frequently implicated in the reported instances of granulocytopenia. Allergic reactions arising from topical application are more common.
ANTIRHEUMATICS, ANALGESICS AND ANTIPYRETICS				
Aspirin	Very low	A_2,A_6	—	Some patients with asthma develop allergy to aspirin. Administration of aspirin to such patients may produce a prompt, persistent and potentially fatal asthmatic attack.
Phenylbutazone	High	A_1	B_2,B_3	
Acetophenetidin	Low	A_1	A_2	

TABLE III.—Type and approximate frequency of allergic or possibly allergic reactions to some commonly used drugs.

*The letters and subscripts refer to the reactions listed under A, B and C in Table I.

1949; Harrington *et al.*, 1953), and the evidence in support of an immunological mechanism is very convincing. Intensive and prolonged therapy

with hydrallazine has given rise to a syndrome which may resemble either rheumatoid arthritis or acute systemic lupus erythematosus. The latter syndrome differs from the spontaneously occurring disease chiefly in that males predominate, renal involvement as judged by urinary findings is missing, subsidence of the syndrome follows when hydrallazine is withdrawn, and the occurrence of 'L.E.' cells in the blood tends to be associated only with the severer clinical manifestations. On the other hand, L.E. cells are commonly seen in the *early* stages of true systemic lupus erythematosus (Dustan *et al.*, 1954; Perry and Schroeder, 1954). Diffuse involvement of the vascular system in allergic reactions to drugs carries a serious prognosis. An allergic reaction to the sulphonamide drugs, and later to iodine, was implicated as a cause of polyarteritis nodosa (Rich, 1942, 1945).

Recently, views regarding the nature of the vascular lesion in such reactions have been modified. The terms hypersensitivity angiitis and allergic granulomatous angiitis (Zeek 1953) and 'allergic' vasculitis (McCombs *et al.*, 1956) have been proposed for reactions of this nature. The latter term is apparently intended to include cases in which biopsy gives microscopic evidence of 'allergic' vasculitis even in the absence of an identifiable allergic cause. The term 'polyarteritis nodosa' is retained for an uncommon, progressive and fatal febrile disease of unknown cause, characterized by involvement of medium-sized vessels and the presence of protean clinical manifestations which commonly include a marked eosinophilia, peripheral neuritis and asthma. The inflammatory vascular changes seen in allergic reactions to drugs tend to involve vessels of smaller, as well as medium, size and are often accompanied by dermatitis, œdema or purpura, and such systemic manifestations as fever and arthralgia. Eosinophilia may occur but it is usually not striking. Although views concerning vascular lesions in allergic reactions to drugs are still in an unsettled state, biopsy of the skin or muscle may be helpful when faced with a confusing clinical syndrome in which allergic reactions to drugs may be playing a part.

TREATMENT

Treatment of allergic reactions to drugs by simple withdrawal of the offender is usually effective. The reaction will subside in a few hours or in a day or two as a rule. Excretion of the drug can be hastened by ensuring a large urinary output. Particular manifestations, such as itching, urticaria, asthma, granulocytopenia, and thrombocytopenia, may require appropriate specific therapy which is usually no different from that appropriate for similar manifestations arising from other causes. Acute reactions characterized by asthma, urticaria and collapse, occurring in combination or singly, may require immediate administration of adrenaline subcutaneously in a dose of 0.3 ml. to 0.5 ml. and, if warranted, the administration of an antihistamine drug intravenously. For this purpose, 10 mg. of diphenhydramine hydrochloride appears to be especially well suited because, in addition to its 'anti-allergic' effect, it has a sedative action. Administration of corticosteroid

drugs or corticotrophin should not be included as an emergency measure in such instances because two to four hours or more must elapse before these agents will exert any recognizable effect on allergic reactions. Furthermore, even when patients are under continuous treatment with these agents, it is doubtful whether they are thereby protected significantly, if at all, from the occurrence of acute and potentially dangerous reactions characterized by the triad of asthma, urticaria and collapse.

The clinical manifestations of most allergic reactions to drugs may be entirely or partially suppressed by the administration of one of the corticosteroids or corticotrophin when given in full therapeutic dosage. Such therapy, however, is probably justified only when the allergic reaction is producing severe discomfort, when the reaction may seriously interfere with some necessary therapeutic or operative procedure on the patient, or when the reaction appears to be of a nature to threaten the patient's life. In very special circumstances one might be justified in continuing administration of a drug in the face of an allergic reaction to the drug and treating the allergic reaction with steroids or corticotrophin. This should not be considered other than a measure of last resort nor should suppression of the clinically recognizable manifestations of the reaction be taken to mean that no damage is taking place. In such circumstances, especially close watch should be kept on the renal, hæmopoietic and hepatic systems.

SUMMARY

Allergic reactions to drugs may have consequences which are out of all proportion to the conditions for which many drugs are given. Because of this, every attempt should be made to eliminate needless administration of drugs and, when possible, to give them under conditions which appear to be least conducive to the development of allergy.

Accordingly, it will probably be in the best interests of the patient to prescribe the fewest number of drugs compatible with effective treatment, to give drugs orally when possible rather than by injection, to question the patient first as to the past occurrence of untoward reactions to drugs and to avoid the topical administration of those drugs which are effective and safe when given by mouth or by injection.

In those instances wherein there is the possibility that the patient may already be allergic, a short-acting, rather than a long-acting preparation should be given.

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ALLERGY AND THE DERMATOLOGIST

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THE clinical features of most of the disorders to be discussed here, with one or two minor exceptions, are well known. Although in all these disorders an allergic mechanism is regularly postulated, in some the evidence of such a mechanism is slight and, even when present, its significance is sometimes doubtful.

The role of allergy in skin disorders has been studied by the following methods:—

(1) Passive transfer tests. (2) Intradermal tests, e.g. tuberculin. (3) Prick and scratch tests. (4) Epidermal patch tests.

The latter two groups of tests are of main interest to the dermatologist and of these by far the more important is the patch test which will be discussed later. The prick and scratch tests, the former of which is probably the more reliable, are often difficult to correlate with the clinical history and indeed, considered apart from this, are of little value as a diagnostic aid and may even be grossly misleading. A careful history is therefore vital as also are elimination and exposure tests to see whether the course of the disease parallels removal of, and re-exposure to, the allergens suspected as its cause. This important question of the significance of the urticarial type of skin test response will be discussed in further detail when considering atopic eczema and urticaria.

HEREDITARY ALLERGY OR ATOPY

This comprises a group of disorders, notably asthma, hay fever and one variety of urticaria. It is possible that in this group should also be included some varieties of migraine. To the dermatologist, however, the most important member of the group is a special form of eczema, often beginning at the age of three to four months on the cheeks and thence spreading to various parts of the body. This form of eczema usually tends to wax and wane until the child is two-and-a-half to three years old. Occasionally, however, particularly in association with a thick and dry skin, it persists into childhood and even to adult life, mainly localized to the flexures, wrists and sides of the neck. Less commonly it may present as a flexural eczema in early childhood for the first time. There appears to be a close relationship between all the members of this group: a strong hereditary

and familial tendency and a common background of abnormality, the most obvious aspects of which are an alteration in the vascular responses of the skin and a tendency to develop hypersensitivity to a wide variety of common substances. It is this background which is inherited and not a specific disease within the group.

ATOPIC ECZEMA

Those who consider that this disorder is allergic in origin and that the skin lesions are the result of an antigen-antibody reaction, base their opinion mainly on two factors: the close association with undeniably allergic conditions such as hay fever, and the sensitivity to numerous allergens as shown by the results of prick and scratch tests, together with the presence of reagins or circulating antibodies which can be passively transferred by the Prausnitz-Küstner technique.

It only remains therefore to discuss the significance of such skin test responses. In the first place, it must be remembered that many responses of this type are non-allergic, being due to trauma or irritation, especially when the skin is highly reactive. The truly allergic reactions can usually be recognized by the large size of the weal and the presence of reagins in the blood, although the absence of the latter by no means excludes allergy. Before we can decide the true significance of those responses which are definitely allergic, the following facts should be considered.

It is now known that many substances, which were formerly thought to sensitize only in rare instances, are capable of sensitizing a large proportion of the population without producing any symptoms. Thus, many infants develop positive skin tests and circulating antibodies to foods such as egg, spinach, and cow's milk without ever manifesting any clinical upset, despite constant exposure to the allergens in question. Many millers react to tests with wheat and barley, many smokers to tobacco and so on, again without producing symptoms (Cohnes, Guild and Rackemann, 1935; Sulzberger, 1933). These are all true allergic responses with circulating antibodies and there is therefore no way of distinguishing them from other allergic responses which may be of clinical significance except by relating them to the history and the course of the disease.

In atopic eczema this can only be done by avoidance of, and re-exposure to, suspected substances to determine whether the eczema improves or worsens accordingly. In evaluating such experiments it must be remembered that the natural history of the disease is to wax and wane, and in many instances, particularly in infants, the disease tends to clear spontaneously. In fact, whenever such experiments have been carefully done, there has been nothing to suggest that the allergens revealed by the skin tests played any part whatever in producing the eczema (Meara, 1955; O'Leary, 1953).

It is quite clear therefore that the increased tendency of atopic individuals to produce multiple sensitivities, far from being the cause of their eczema,

is merely a part of their atopic background, just as are the abnormal responses of their skin vessels to changes in temperature (Weber, Roth and Kierland, 1955). It is interesting to note that many of the sensitivities exhibited by babies to such things as egg white and cow's milk often disappear spontaneously as they get older and this, together with the tendency for many infantile eczemas to clear spontaneously, probably accounts for many of the so-called 'cures' from specific desensitization. For all these reasons, the value of such procedures as specific desensitization and elimination diets in atopic eczema is, to say the least, doubtful.

URTICARIA

Urticaria may be provoked by many different stimuli, only some of which are of an allergic nature and these often bear no apparent relation to the group of hereditary allergy or atopy. Perhaps the commonest truly allergic form of urticaria is that produced by drugs, especially penicillin, aspirin and salicylates. Almost any drug, however, may produce urticaria, and in this age of rapid multiplication of drugs it is essential to inquire fully about any drugs that may have been given. Aspirin and salicylates may be disguised in many proprietary preparations. Penicillin may be overlooked as a possible cause unless specific inquiries are made about the use of throat lozenges, ointment or cream containing penicillin. The possibility of penicillin by injection as a cause of urticaria may be missed unless it is borne in mind that there is often a latent interval of a week or two between the last injection of the penicillin and the onset of the urticaria. It is also important to remember that drug urticaria may result from the use of vaginal pessaries. Drug urticaria is often acute but may sometimes, and particularly with penicillin, set up an urticarial state which lasts for many weeks or months. On occasion, drug urticaria merges into anaphylactoid purpura.

Amongst other causes of urticaria, in which an allergic mechanism is postulated, must be mentioned foods, which are often blamed and are rarely responsible. When they are the cause, the urticaria is usually acute and the sudden onset and just as sudden disappearance nearly always leave a patient in little doubt as to the cause of his eruption, particularly if it has occurred on other occasions. Gastroenteritis is sometimes followed by acute urticaria but whether this is an allergic or a direct toxic effect is uncertain. Toxic foci are often blamed, particularly in chronic cases, but there is little real evidence to support this theory in most instances.

Other less common causes of allergic urticaria are infestation with parasites, of which latent scabies is probably the commonest external, and ascaris the commonest internal, example. Urticaria may also occur as an abnormal reaction to heat, light or cold. Although some authorities consider that these last three are the result of allergic mechanisms, the evidence at present is conflicting.

Diagnosis.—Once again the significance of intradermal skin tests of the

prick or scratch type must be discussed, and one might think that since such tests actually produce the type of lesion from which the patient is suffering, they might be just as useful as, by analogy, the patch test is in allergic contact dermatitis. Nothing could be further from the truth. It is a sad fact that skin tests are virtually worthless in urticaria and as eminent an authority as Sulzberger (1940) states that he is

'in complete agreement with all those dermatologists and allergists who do not perform skin tests in urticaria except as a research measure—or as a very last resort or possibly as a placebo forced upon the physician by the widespread and profound misconceptions of the lay public on the subject of allergy'.

There are two main reasons for this, apart from the difficulties already mentioned when discussing atopic eczema. In the first place, innumerable substances which can have no possible significance give positive reactions to scratch or prick tests in urticaria, probably because the skin is in a hyper-reactive state. Secondly, even when an allergic cause is known and proved by avoidance and exposure, it may fail to give positive skin test reactions. In fact, if on very rare occasions skin tests ever do give any help it is almost invariably true that their significance can only be appreciated with such help from the history that this alone would suffice to make the diagnosis.

ALLERGIC CONTACT DERMATITIS

This disorder is, without doubt, by far the most important aspect of allergy to the dermatologist since it is the result of direct contact between the skin and the offending allergen which may be anything from an exceedingly complex substance, such as a plant oleoresin, to the very simplest of chemicals such as formaldehyde. The actual allergic mechanism is unknown but circumstantial evidence for its existence is very strong.

The sensitizing capacity of different substances varies greatly and allergic contact dermatitis from some, e.g. paraffin wax, is virtually unknown, whilst others such as dinitrochlorbenzene can, by the application on one occasion of a single drop of a 10 per cent. solution, sensitize the entire skin on some 60 per cent. of persons thus treated (Sulzberger and Baer, 1938). Susceptibility to sensitization and the degree of sensitivity, once acquired, vary greatly in different individuals. Once established, such sensitivity, to which there appears to be little hereditary predisposition, is likely to last for life or at least for many years. Repeated exposures to the antigen in question are not necessary to maintain this sensitivity, and the epidermis, to which the antibodies are in some way thought to be fixed, possesses some sort of 'cell memory'. This is all the more remarkable when one considers the constant replacement of these cells which means that even in a few years innumerable generations of new cells have succeeded those which were originally sensitized.

The antigen-antibody reaction is remarkably specific and in most instances will distinguish very small changes in the molecular structure of the allergen. At times, however, the specificity seems to be determined not by the entire molecule but by some side-chain or group in a certain position and this

leads to the phenomenon of cross-sensitivity (Meltzer and Baer, 1949). This means that a patient, being sensitive to a given substance, e.g. benzocaine, may also be sensitive to other substances with certain similarities of structure, such as sulphonamides, or paraphenylene diamine hair dyes, even though these have never before been encountered by the patient. In these examples sensitivity is to an amino-group in the para position on the benzene nucleus.

Diagnosis.—The epidermal patch test provides more useful and positive information than any of the other skin tests used in allergy but, despite this, it must be emphasized once again that the history is the foundation upon which diagnosis is based, particularly since most instances of exogenous dermatitis are due to primary irritant substances and not to allergic sensitization. Furthermore, the range of possible antigens is almost limitless and so the intelligent cooperation of the patient is essential in deciding which tests should be made, unless the site of the dermatitis suggests possible lines of inquiry. In particular, it is important to discover, so far as possible, where the eruption began. For instance, lesions occurring on a woman's thighs under her suspenders suggest nickel as the sensitizer, particularly if other areas of contact with nickel alloys such as the ear lobes, under brassiere clips and watch bands, are also sites of dermatitis (Wilson, 1956). Lesions on feet and legs may be produced by shoes, nylon stockings and so on. A facial dermatitis, in addition to the obvious causes such as cosmetics or other local applications, always suggests the possibility of sensitivity to flowers. If it particularly affects the eyelids, nail lacquers and, in the case of a nurse, antibiotics such as streptomycin should be considered. These are, of course, only a few of the commoner examples. Last, but far from least, is the possibility that some local application may be responsible, particularly if it is known to be a potential sensitizer, e.g. a cream or ointment containing antipruritics such as the antihistamines, local anæsthetics such as benzocaine, or antibiotics such as penicillin.

Not infrequently the history strongly suggests a possible cause but lesions are also present in areas where contact with the allergen has not occurred. This need not invalidate the diagnosis for, when an allergic dermatitis has been produced for a certain length of time, and this may vary from weeks to years in different individuals, the skin finally undergoes some unknown change which enables it to produce eczematous lesions without any further stimulus from the substance which originally caused the dermatitis. This is a serious state of affairs because it means that, even if the allergen is thereafter avoided completely, recurrent eczema may continue almost indefinitely. Some substances seem more liable to produce this state of affairs than others, and a notorious example is nickel which is doubly unfortunate since it is one of the commonest causes of allergic contact dermatitis. This widespread sensitization of the skin also provides a grievous trap in diagnosis since the portion of inflamed skin offered by the patient for inspection may be secondary to a primary focus elsewhere.

The practised dermatologist, if in doubt, will not make the mistake of asking whether the patient has trouble elsewhere on the skin, thus usually initiating a somewhat sterile and acrimonious debate, but will ask to see all the skin without more ado.

Finally, the patch test. Incorrectly done, this can be very misleading and it is sufficiently important to merit description in some detail.

Solid substances may be applied direct to the skin, whilst a ¼-in. (6-mm.) square of gauze is moistened with any liquid to be tested. Over this is placed a square of cellophane or oiled silk 1½ inches (4 cm.) square, the whole then being held firmly against the skin with adhesive strapping. A control patch consisting of everything but the substance being tested must also be done for comparison. The patches, a number of which may be done at once, should only be applied to normal skin, preferably on the back. If the dermatitis is very acute or widespread, it is advisable to delay their application until the inflammation has begun to subside. It is extremely important to ensure that the substance being tested is not used in a concentration in which it might act as a primary irritant, and tables of suitable concentrations of allergens are published (Schwartz, Tulipan, and Peck, 1947). In general the weakest possible concentration, i.e. 1 per cent. or so, should be used. In any case, if a patient is really sensitive to a substance, it does not require a strong solution to elicit a response.

Patches should be removed and read after forty-eight hours and a positive reaction may be anything from a patch of erythema and papulation to a group of vesicles with considerable erythema and œdema. Erythema alone should make one suspect a non-specific irritant reaction and re-reading after 96 hours helps one to separate these cases because a true allergic response will be unchanged or even more obvious by then, whilst an irritant one will probably have disappeared. Occasionally, when the sensitivity is extreme, the application of the patch test will cause a flare-up of all affected areas. On rare occasions a negative test does not exclude sensitivity since it does not necessarily reproduce the conditions of exposure: e.g. sweat, friction, concentration. Conversely, a positive reaction does not necessarily mean that the substance is causing the patient's disease.

The ten commonest causes of allergic contact dermatitis seen at St. John's Hospital for Diseases of the Skin during the past four years are nickel, chromates, turpentine, lipstick, flowers, rubber, synthetic resins, antihistamines, antibiotics and proprietary ointments, of which nickel was by far the commonest, the others varying from year to year (Calnan, personal communication).

DRUG ERUPTIONS

These are being fully discussed by Dr. Lowell on p. 673, but there are two eruptions which do not appear to be well recognized by the profession as a whole. The first is the fairly uncommon, but characteristic, purpuric eruption caused by drugs of the carbromal class: e.g. 'sedormid', 'persomnia' (Borrie, 1955). The lesions first appear on the feet and ankles and, if the drug continues to be taken, extend up the limbs and trunk until finally the whole body may be involved. The minute appearance of the lesions is highly characteristic: instead of the bright red macules of classical purpura, one sees large numbers of small, often pinhead-sized lesions

which are brownish-red in colour and over which is usually a certain amount of fine scaling. Itching is almost always severe. When the drug is stopped, the lesions usually clear within three to four weeks, but reappear within twenty-four hours should it again be taken. The other drug eruption which often escapes recognition is the uncommon so-called fixed drug eruption (Abramowitz and Nour, 1937). The typical lesions are sharply circumscribed areas of erythema often with a dusky hue. They are remarkable because every time the drug is taken these areas react with intense itching, erythema and sometimes blistering, whilst the remainder of the skin remains unaffected. Each subsequent exposure leads to a further reaction in exactly the same areas. Fresh lesions may, of course, appear if the drug continues to be taken. A number of drugs may produce this effect, but in practice phenolphthalein accounts for most eruptions of this kind, although often no cause can be found. Phenolphthalein is contained in many proprietary laxatives, chocolate-coated and otherwise. Other less common causes are 'antipyrin' and barbiturates.

Finally, a diagnostic problem. Dermatologists are constantly being asked whether a patient's eczematous eruption is due to drugs which he is taking. In the vast majority of such cases the eczema is confined to certain areas and, while the drug is still being administered, shows little tendency to spread rapidly. In these cases the drug is almost invariably not at fault. In the true eczematous types of allergic drug reaction, such as those due to arsenic and penicillin, once the eruption appears it progresses with great rapidity and usually ends up as an exfoliative dermatitis even if the drug is quickly withdrawn. Careful consideration of the history alone will therefore enable the distinction to be made in most instances.

BACTERIAL ALLERGY

Allergy to various micro-organisms or their products has for many years been advanced as the cause of innumerable skin diseases of unknown etiology. The available data, however, do little to justify such an assumption. Much of what has been put forward as evidence in favour of such claims has been the result of treatment designed to remove such 'toxic foci' or to desensitize the patient to the harmful products of his organisms. It is very doubtful whether many of the successes thus claimed would stand up to statistical analysis when considered in relation to the natural history of the diseases in question.

There is, however, strong circumstantial evidence deriving from a study of the natural history of known infections, e.g. tuberculosis, that allergic responses to micro-organisms or their products do occur, the so-called tuberculides. There is, for instance, good reason for believing that erythema nodosum may be an allergic response to many different infections: e.g. streptococcal tonsillitis, primary tuberculosis, leprosy, coccidioidomycosis and sometimes, apparently, drugs. Superficial fungus infection may cause allergic or 'id' reactions. Two of the most characteristic are the profuse

eruption of tiny follicular spiny lesions sometimes occurring in conjunction with a pustular animal ringworm kerion and the rather more common vesicular eruption affecting the hands, which is secondary to an acute and severe tinea pedis (Calnan, 1956). It is characteristic of bacterial allergy that it is seldom if ever possible to regrow the causal organism from the allergic reaction produced, and it is thought that this is in some way related to an overwhelming response by the body which kills off the causal organism.

VASCULAR ALLERGY

In addition to the foregoing disorders, most of which are known to be associated with an allergic mechanism, there are several conditions in which such an etiology is strongly suspected although it has never been proved. One interesting group of disorders, in all of which are to be found certain histological changes in the small blood vessels which suggest that they may have a common etiology, includes polyarteritis nodosa; a condition known as allergic vasculitis in which purpuric, and also at times erythematous, nodular and necrotic lesions appear in crops on the lower limbs; anaphylactoid purpura; erythema nodosum and erythema multiforme. These changes are thought to have a possible allergic background because certain experimentally produced allergic lesions in animals, such as the Arthus and Sanarelli-Shwartzman reactions, are accompanied by vascular changes; in addition, sensitizing rabbits with injections of foreign serum produces lesions in the small arteries which closely resemble those seen in polyarteritis nodosa (Rich and Gregory, 1943).

Furthermore, erythema multiforme and erythema nodosum can both be produced by drugs and certain infections in circumstances which strongly suggest an allergic background. Although there is even less real evidence to support it, there has for many years been a body of opinion which considers systemic lupus erythematosus to have an allergic basis. The abnormal serum globulins, the positive Coombs test and the fact that a disorder indistinguishable from systemic lupus erythematosus has been produced by hydrallazine (Dunstan *et al.*, 1954) have all been regarded as pointers in this direction.

TREATMENT

Only those aspects of treatment which are specifically aimed at modifying the antigen-antibody reaction or its effects will be discussed here.

Specific desensitization.—The scope of this is automatically limited by the necessity of discovering the allergen responsible for the disease. In the two disorders in which it should be most useful to the dermatologist therefore, i.e. allergic contact dermatitis and drug eruptions, it is unfortunately of little value. In many of the reports of successful desensitization in drug eruptions and contact dermatitis the diagnosis has been questionable. Even if patients exhibiting severe drug eruptions can very occasionally be desensitized, the degree of tolerance which is achieved is usually temporary and probably of little practical value. In the vast majority of such cases,

desensitization is impossible. Desensitizing patients with allergic contact dermatitis often cannot even be attempted since the allergens may be too toxic to be administered. Even when it is possible, opinions vary widely as to its efficacy but are generally unfavourable. Once again, even if a state of desensitivity can be produced, it is only temporary (Wood, 1956). This is even true of hay fever where desensitization is often effective but injections have nevertheless to be repeated every year. The only reliable and reasonable treatment for the vast majority of patients therefore is avoidance of the causal allergen.

Antihistamines.—When the allergic reaction results in the liberation of histamine or histamine-like substances as in urticaria, one can attempt to influence it with antihistamine drugs. The amount of such a drug which is required to abolish a standard histamine weal may vary greatly in different individuals (Warin, 1950) and it is probably true to say that whenever such drugs fail to suppress clinical urticaria it is because the dosage is too low. Unfortunately it is not always possible to give the required amount because side-effects become troublesome. If the disease is not controlled, however, the drug should not be abandoned until the dose has been increased to the point at which such side-effects appear. Antihistamine drugs are of little or no value, except perhaps as mild sedatives, in the other conditions which have been discussed here.

Apart from trying to abolish the antigen-antibody reaction or blocking the action of H-substance where appropriate, the other way in which the disease process can be influenced is by minimizing the ill-effects of the allergic reaction on the sensitized tissues. This can be done with cortisone and allied steroids but since their reaction is merely a general anti-inflammatory one, and not limited to the allergic mechanism alone, it will not be considered here.

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HAY FEVER

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DURING the month of June the patient with hay fever is miserable. It is intended briefly to describe why this is so and what remedies are available for treatment. Summer hay fever may not be a killing disease but it can make life miserable for the unfortunate victim.

Hay fever is not a new complaint. Herberden (1803) described it, Bostock (1828) noted that asthma was a common complication, Blackley (1873) scientifically investigated the cause and Noon (1911) successfully treated hay fever patients by a series of graded injections.

DEFINITION

'Hay fever' is a term which often has little scientific meaning. It should be used to describe the seasonal symptoms occurring in patients sensitive to grass pollens, although the term can be objected to because the symptoms are not due to hay and no fever occurs. 'Grass pollinosis' is a good descriptive term, whilst 'summer hay fever' gives a better idea of the complaint than 'hay fever' which is a term used loosely in describing any patient with undue sneezing and rhinorrhœa.

'Hay fever' can be defined as the seasonal symptoms of irritation of the conjunctivæ, with rhinorrhœa and sneezing, with or without asthma, occurring in those patients sensitive to grass pollen. Other symptoms may occur. Sometimes there is an irritating sore throat which is difficult to distinguish from the feeling produced by an infective throat. Epistaxis may occur in association with the repeated sneezing. Also, children playing in the grass may produce urticaria because the pollen gets into minute abrasions on the skin.

The only important cause of seasonal symptoms of hay fever in Great Britain is grass pollen, and the grass pollen season is relatively short (Hyde, 1952). It lasts usually from the first week in June to mid-July. Symptoms may start earlier and go on later but any symptoms occurring outside the period from May to August are due to causes other than grass pollen. Tree pollens, flower and weed pollens may occasionally cause seasonal symptoms either by themselves or added to the symptoms of a grass-pollen sensitivity.

DIAGNOSIS

It is quite a mistaken idea that allergy is diagnosed by skin tests. Skin tests only confirm what the history should already have indicated. The diagnosis of seasonal hay fever due to grass pollinosis is simple so long as an accurate history is taken. There are two important points which should be obtained

in every history: (i) the seasonal periodicity of the symptoms and (ii) their character. In dealing with the seasonal periodicity some patients are most accurate as to the time of the start and finish of their symptoms. This in itself is in favour of a grass-pollen sensitivity, because the flowering period of the grasses varies but little from year to year (Hyde, 1956). Children tend to be vague about dates, but questions as to whether the symptoms persisted after the end of term or during holidays in August will generally bring out the necessary information. If there is any doubt as to dates, nothing will be lost by making a patient keep a daily chart or diary of the symptoms from the time they start until they have finished. When the symptoms are at their worst in, or almost confined to, June and July, it is likely that they are due to a grass pollen sensitivity. When they occur from July to September the symptoms are certainly not due to grass pollens. In either case the story will be that the complaint occurs 'in the summer months when it is hot'. The late summer symptoms are almost always caused by a mould spore sensitivity (generally *Cladosporium*). The symptoms from a *fungal* sensitivity, however, are different in that besides the peak symptoms occurring at least a month later there is no eye irritation as in grass-pollen sensitivity. It must therefore be stressed that with hay fever there is always eye irritation to a greater or lesser degree, whereas with a mould spore sensitivity uncomplicated by a pollen sensitivity, eye irritation does not occur.

Grass-pollen sensitivity is the commonest seasonal inhalant allergic problem. Even so, other pollens and also fungal spores may cause inhalant sensitivities. The patient who has typical hay fever in June and July and then has asthma in August and September, has almost certainly asthma due to a mould spore sensitivity, although my experience is that this is generally treated as infective asthma. The point must be stressed that the seasonal hay fever patient does not (and this is perhaps surprising) become infected. Purulent sinusitis with a seasonal hay fever is very rare. So, too, when asthma occurs in true hay fever it is allergic and not infective in origin. This point is important for many reasons. The results of specific injection treatment of allergic asthma are good, and the prognosis is also good. In infective asthma in adults, although the immediate results of treatment may be good the ultimate results are poor owing to increasing dyspnœa from emphysema.

SKIN TESTS

When the clinician is quite clear in his diagnosis, he may then carry out skin tests. The minimal number is two though many more may be done. Pollen solutions should never be used intradermally. (Incidentally I consider it a good rule never to test intradermally at all when investigating allergic complaints.)

A recently qualified doctor was asked to treat a patient with seasonal asthma. He did not know how to set about this but thought he would make a good start by proving the diagnosis. He found a bottle of 20,000-unit pollen extract. He injected a small amount (0.1 ml.). The patient developed a very marked local reaction and, five minutes later, severe asthma and then became unconscious. In the simple

prick skin test method (Squire, 1950) about five-millionths of a cm. are introduced, so the intradermal test had introduced 20,000 times too great a dose.

The *prick method* of skin testing consists in pricking through the testing solution on the forearm so that the prick can just be felt but no blood is produced. In a pollen-sensitive patient an irritating weal begins to form in three minutes and is maximal at about fifteen minutes. A control test is made by a prick through a drop of normal saline: This should always give a negative response, although in a dermographic patient a non-specific response is produced by all the tests.

The size of the skin response is not an indication of the degree of sensitivity. A positive skin response may appear ten years before clinical sensitivity occurs. Sometimes the positive skin response may never become clinically important unless there are exceptional quantitative conditions of pollen. I myself have a strong skin response to grass pollen when using the prick method, but hay fever is not normally apparent at the height of the pollen cloud. Yet the very high pollen content of the pollen-collecting room at the pollen farm will produce acute hay fever. After injection treatment the patient's skin reactions tend to diminish in size but will often remain positive for twenty years after all traces of clinical sensitivity have disappeared.

The minimal number of skin tests to prove a grass-pollen sensitivity is two: a mixed grass-pollen extract and a control carbol-saline test. Some patients seem much more satisfied if tested for ten or twenty different grass pollens. In Great Britain this seems quite unnecessary. Timothy grass (*Phleum pratense*) and Cocksfoot (*Dactylis glomerata*) are the two most profuse pollen producers. A patient sensitive to one will be sensitive to the other. Either pollen by itself or a mixture of the two pollens can be used for treatment. In addition to skin tests, immunological tests (Augustin, 1955) and clinical trials (Frankland and Augustin, 1954; Frankland 1955b) have shown that either pollen can be used for treatment. Patients with seasonal hay fever may not be sensitive to some of the rarer grass pollens or to a grass pollen not found in this country. There is therefore a considerable degree of antigenic specificity of the different grass pollens, but for practical purposes this does not matter and it is only necessary to use in diagnosis and treatment a common abundant grass pollen.

Tree pollens in the spring occasionally cause rhinitis and asthma. Tree-pollen sensitivity by itself is very rare. Occasionally, alder, hazel, willow, silver birch, elm, plane or oak cause symptoms. The importance of tree-pollen sensitivity in Britain has recently been reviewed by Hyde (1956). Silver birch and plane trees should perhaps be borne in mind as possible causes of spring hay fever. Pine pollen does not sensitize: a finding that is general throughout the world (Ordman, 1945), although some of the closely related pollens from cypresses (*Cupressine*) and yew trees occasionally cause clinical symptoms.

Weeds and flowers may cause trouble. In this country, unlike the United

States, we have no ragweed. Plantain and sorrel reach their peak pollination at the time the grasses begin to pollinate. *Chenopodium* (goosefoot) is locally abundant and may cause some symptoms. A patient was recently seen who was sensitive only to nettle pollen, but all these sensitivities are rare. The *compositæ* family is a large one. *Artemesia* (ragwort), which is a plentiful weed, produces a very fine pollen and probably causes some allergic symptoms towards the end of the grass pollen season. Most other members of the daisy family have a sticky heavy pollen which is not windborne and allergically they are not important. Pyrethrum in insect sprays and powders may cause non-seasonal allergic symptoms.

DIFFERENTIAL DIAGNOSIS

It must not be forgotten that to many doctors and patients the term 'hay fever' is a vague descriptive term for a nose that runs excessively, or becomes blocked or sneezes, or any combination of these symptoms. Sometimes the condition is called catarrh. Whatever the term used, the cause is often not known. A patient sneezes unduly and comes for advice to find whether a definite (allergic) cause can be found. In this short article it is not intended to differentiate between all the causes of rhinitis when they are non-allergic. A seasonal and/or an environmental incidence of rhinitis symptoms is always suggestive of an allergic cause. If the symptoms are non-seasonal but made worse by stuffy rooms, change of temperature, tobacco smoke, or strong smells, usually no specific allergic cause is found. Sneezing on awaking or on getting out of bed often occurs in patients with non-specific rhinitis. Fumes, face powders, and especially washing powders, easily irritate the nasal mucosa. The various components of household dust may act both specifically and non-specifically as an irritant. The pale, wet swollen turbinates of an allergic nose are supposed to have quite a typical appearance. Yet many cases of rhinitis have just this appearance and no allergic cause can be found for the symptoms. Eosinophilic cells in the secretion are suggestive of an allergic etiology, but it must be remembered that nasal polypi generally contain many eosinophils, yet usually no direct allergic cause can be found for them.

Antihistamines may dry the wet mucosa but this in no way confirms that the rhinitis is allergic (Frankland, 1953). The drug may have given relief because of its atropine-like effect in drying the nasal mucosa. The marked soporific effect of many of the antihistamines may also be beneficial to the patient but again in no way confirms an allergic cause for the symptoms. Steroids taken systemically help the patient with severe non-allergic and allergic rhinitis and cause polypi to disappear. The therapeutic result of palliative treatment in no way confirms that the condition is allergic.

TREATMENT

The basic treatment of allergic diseases is to find the cause and eliminate it if possible. If the only cause is a cat, it is easy to get rid of the cat. It is easy

to replace a feather pillow with a latex pillow when dust is an important cause of symptoms. It is impossible to get away from grass pollens in the summer, although there is less grass pollen in the centre of a large town than in the country. The sea front with the wind off the sea is ideal but a caravan in a field near the sea front may be responsible for a spoilt holiday for the hay fever subject. Open bedroom windows at night and open windows in the car when travelling will increase the local pollen concentration.

PALLIATIVE TREATMENT

Nasal drops are of some help to patients, particularly when the nasal airway is obstructed. Many of the nasal drops now contain a steroid as well as a

Proprietary name	Approved name	Colour	Manufacturer	Dose per tablet
Actidil	Triprolidine	White	Burroughs Wellcome	2.5 mg.
Ambodryl	Bromazine	Red	Parke Davis	25 mg.
Ancolan	Meclozine	White	British Drug Houses	25 mg.
Anthisan	Mepyramine maleate	Green	May & Baker	50 and 100 mg.
Antistin	Antazoline	White	Ciba	100 mg.
Benadryl	Diphenhydramine	Red	Parke Davis	25 and 50 mg.
Ben-hist	Antazoline	White	Bencard	100 mg.
Diatrin	Methaphenilene	White	William R. Warner	50 mg.
Dibistin		Cream	Ciba	Antistin 50 mg. Pyribenzamine 25 mg.
Diparelene	Chlorcyclizine hydrochloride	Yellow	Abbott	50 mg.
Histantin	Chlorcyclizine hydrochloride	White	Burroughs Wellcome	50 mg.
Histostab	Antazoline	White	Boots	100 mg.
Phenergan	Promethazine	Blue	May & Baker	10 and 25 mg.
Piriton	Chlorpheniramine	Yellow	Allen and Hanburys	4 mg.
Pyribenzamine	Tripelennamine	Pale blue	Ciba	50 mg.
Sandosten	Thenalidine	White	Sandoz	25 mg.
Synopen	Halopyramine	White	Geigy	25 mg.
Thephorin	Phenindamine	Yellow	Roche	25 mg.
Vibazine	Buclizine	White	Pfizer	25 mg.

TABLE I.—British antihistamine preparations.

decongestant. Cortisone and hydrocortisone *snuff* has also been used, but a controlled trial comparing this form of treatment with other symptomatic treatment will be necessary before it can be stated that in hydrocortisone snuff an advance in symptomatic treatment has been made.

Decongestant *eye-drops* containing hydrocortisone or an antihistamine may also be used. *Dark glasses* are particularly helpful to fair-skinned people.

The mild case of hay fever receives definite benefit from *antihistamine* drugs. Their use in general does not increase the incidence of asthma (Frankland and Gorrill, 1953), although occasionally an antihistamine or even corticotrophin will produce asthma. Table I gives a list of the antihistamine preparations commonly available in Great Britain. It does not

include those sold for travel sickness, or the many cough medicines, lotions, ointments and nasal drops that contain an antihistamine preparation. Sedative and gastric irritant effects often preclude the effective use of the antihistamine drugs in the symptomatic relief of hay fever. Most patients now know of the soporific effects to be expected from taking these drugs.

There would seem to be a definite place for short-term *steroid therapy* in those patients who have severe asthma in association with their hay fever in the summer, but the contraindications and possible complications should always be considered before starting this form of treatment. A patient was seen last year who developed a Cushingoid syndrome with fluid retention after using hydrocortisone snuff for six weeks. This at least indicated that the drug was being absorbed.

SPECIFIC TREATMENT

The specific injection therapy for cases of seasonal hay fever has changed little over the past few years. The injections are given pre-seasonally, starting in the winter months and finishing just before the symptoms normally begin. A few injections, and therefore a low dose of pollen extract, give a poor result (Frankland, 1955a). The higher the dose reached the better the result, but many injections have to be given because unless the first doses are very small and the increase in dosage is gradual, severe general reactions may occur. Details of injection treatment are available from the various manufacturers of pollen extracts. The injections should be carried out for at least three years, but, surprisingly, patients often prefer to have injections than to have hay fever. This particularly applies to those patients who obtain no relief from palliative drugs and who have asthma associated with the hay fever.

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ALLERGY IN CHILDHOOD

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THERE are certain well-defined allergic disorders, and others into which an allergic element probably enters, which between them supply some of the most tiresome and intractable problems in childhood. On the other hand, allergy has been made into a bogy and very often blamed by parents, and sometimes by doctors, for many of the vague recurrent symptoms from which some children suffer, and which are in fact largely or entirely subjective.

Asthma, hay fever, allergic rhinitis, urticaria and eczema are the common allergic disorders and are all difficult to treat, but do eventually respond to care. Spasmodic or asthmatic bronchitis is another condition in which allergy may play a part: it may, or may not, be an entity. Milk and other food allergies do not appear to be common or of great importance in Great Britain, although they are more often diagnosed in North America.

This by no means completes the list of diseases of childhood in which allergy plays a part, but comprises merely those which are definitely due to allergy and which provide a constantly recurring problem to the practitioner.

INHERITANCE

Any individual may eventually produce an allergic response as a result of repeated exposure to an allergen, but the susceptibility of individuals to allergy varies greatly. There is little doubt that this depends upon a constitutional predisposition that is genetically determined. A history of some form of allergy in close relatives is almost always obtainable in any case of allergy in childhood, and particularly in asthma, eczema and hay fever. A person with a history of allergy will not necessarily pass on the same type of allergy to his own children, but it is likely that some of his children will have a greater susceptibility to any form of allergy than the children of non-allergic persons; if both parents have some allergic complaint, then the likelihood of allergic disorders appearing among their progeny is considerably greater.

DESENSITIZATION

Desensitization, or strictly speaking hyposensitization, is brought about by the subcutaneous injection of small quantities of the allergen in gradually increasing amounts until the optimum result is obtained. Sensitivity gradually returns if the injections are discontinued. It is therefore necessary, if the treatment has shown any success, to continue to give the injections

indefinitely at intervals of not more than four weeks, or to repeat the course each year.

Desensitization has proved of definite value in conditions in which there is a known specific allergen. It is of less value when the patient is sensitive to a whole group of allied substances, and of little value when there is sensitivity to a variety of different types of allergen.

Desensitization does not do away with the need for avoidance of the allergen and this, if at all possible, should remain the primary aim. Complete separation from the allergen is the most effective method of treatment, but this is usually impracticable. All too often the parents' observations on the cause of the allergy are based on preconceived beliefs, or prove to be fallacious for other reasons, but ascertainment of the substance to which the child is allergic may be a matter of simple observation and careful history taking.

A recent example of the value of this occurred in the case of a small child with newly developed but severe asthma, whose father had also developed asthma at about the same time. The family, according to the mother's history, lived in a damp prefabricated house, the inside walls of which were covered with a mould. It was ascertained that neither father nor child had symptoms if they slept away from home. Skin testing showed that the child was sensitive to moulds and a course of desensitization against moulds brought some relief of symptoms. Both father and child remained completely free of symptoms after the local housing authority arranged for their transfer to a new housing estate.

Elimination diets are used, particularly in the United States, in the investigation of the causative factors in infantile eczema and food allergy. They are probably useful in food allergy, but of little value in established eczema, in which the sensitive skin reacts to a large variety of allergens. The basis of the elimination diet is the use of some substance to which allergy hardly ever occurs, such as rice in older children and soya-bean milk preparations in infancy. It is often a prolonged and tedious process to detect the foods responsible for the allergy by this method and the final results seldom repay the time and effort spent in the investigation.

Skin testing is a relatively quick and simple method of detecting possible allergens but, whilst sometimes helpful, it often adds little to the factors already known from the history. This is because skin sensitivity does not necessarily reflect a similar sensitivity of the bronchial tree or of mucous membrances, and because skin sensitivity may be present to a wide variety of substances. It is not intended here to go into details of the techniques of skin testing and desensitization—which may be obtained from the manufacturers of the skin testing and desensitizing solutions—but a word of warning may not be out of place concerning the dangers. Skin testing by the scratch technique is entirely safe and carries no risk. Intradermal testing is more sensitive and perhaps excessively so, but it does carry a slight risk of inducing a severe reaction in a highly sensitive small child; although generally quite safe, it should be used with caution. Similarly, the early stages of desensitization may be followed by severe reactions in small children, even though the manufacturer's perfectly sound instructions

are carefully followed. It is therefore wise to have a syringe and adrenaline handy and to keep a child under observation for at least an hour after the injection, and, if the child is known to be unusually sensitive, to proceed even more cautiously than recommended with increases in the size of the injection.

ASTHMA

The association of asthma with infantile eczema, as in the eczema-asthma-prurigo syndrome, is well known, and it is relatively safe to assume that recurrent respiratory symptoms, unassociated with obvious infection, in a child who has, or has had, infantile eczema are due to asthma. Otherwise, in infants and young children the diagnosis may be difficult and no certain conclusion may be possible over the course of a year or so, until typical symptoms appear. A history of some form of allergy in the parents or other members of the family is a useful indication that asthma may be the correct diagnosis in an infant who has a tendency to wheeze and cough for a number of days after any cold, or even after a simple change in the weather. In other cases the infant may have attacks in which he wakes at night, restless and crying, with perhaps a cough which disappears during the day.

After the passage of a year or two, and in older children, the attacks become more typical of classical asthma, with the sudden onset, generally at night, of tightness of the chest, dyspnœa and wheezing. In some children the attacks are preceded by a nasal discharge, which is generally called a cold, and whilst this may be the cause in some instances, it is probably more often due to allergic rhinitis. Exercise and emotion and cold, windy or foggy weather may precipitate attacks, as well as exposure to any known allergen. It is in fact rare to obtain a history of attacks clearly attributable to the latter cause. The mother sometimes notices, however, that the child begins to wheeze if he has been following her round as she sweeps out the house; occasionally, playing with animals, especially birds or cats, is followed by wheezing and tightness in the chest. Ordinary house dust is probably the most common allergen, or rather group of allergens, responsible for asthma in this country, and feathers, animal hair and wool are probably the most important separate components of this group.

Emotional factors, especially in the older child, are of the first importance not merely in precipitating attacks, as happens after a row at home or before some exciting event, but also probably in increasing the susceptibility of an already predisposed child to develop symptoms. Anxiety over school work, jealousy of other children at home, a disturbed home life or a broken home can contribute greatly to the severity of the disease and frequency of attacks. There is, of course, almost inevitably some tension and anxiety in any household in which there is a child suffering from frequent attacks of asthma, but in some this is carried to a pitch at which it becomes the main contributory cause of the attacks. Furthermore, in these the parents' expectancy of attacks is so high that the child becomes conditioned to respond to any unpleasant or awkward situation by the development of an

attack. Over-tiredness is another factor which should not be overlooked.

During an attack the young child may only have rather more evidence of difficulty in breathing than would be found in a mild bronchitis or pneumonia. He may be restless, the alæ nasi may be working and the lower ribs and intercostal spaces be drawn in on inspiration; the air entry is likely to be poor and the breath sounds wheezy.

The older child with chronic asthma is thin, with high shoulders, a mild dorsal kyphosis, a narrow pinched nose and anxious expression. The chest is barrel-shaped, or long and narrow and hyper-resonant to percussion; it moves very badly and the air entry is poor and the breath sounds wheezy. During an attack the child sits up in bed, with an apprehensive look on the face; the alæ nasi are working and there is little movement of the chest itself. The lungs are full of squeaky and high-pitched rhonchi.

TREATMENT OF ASTHMA

In any household where there is an asthmatic child it is difficult to balance the physical steps necessary to prevent attacks with the need to avoid the development of an atmosphere of fussing and anxiety. Knowledge and understanding of the parents' personalities are required by the practitioner. If the parents tend to be over-anxious it is likely that the less the stress that is laid upon all the precautions to be taken, the better will be the course. Such parents, in their desire to do everything they should, often develop an obsessional carefulness in regard to the child and tire themselves out in their efforts. Reassurance is therefore of first importance and it is worth emphasizing that, with the rarest exceptions, improvement always occurs with increasing age, and that no lasting pulmonary damage will occur. It is also wise to ascertain that the parents, as well as the child, have adequate sleep and do not get up several times every night to ensure that the child is all right.

It is certainly advisable to remove all feather-containing objects from the child's own room and, so far as possible, from the house. This implies the replacement of feather mattresses, pillows, eiderdowns and cushions with kapok, foam rubber or synthetic fabric. The child's own room should be as bare as possible of any dust-collecting hangings and carpets and should not be used for the storage of clothing or other materials. Wool is sometimes responsible for symptoms, and cotton, or another covering, should be put over the blankets on the bed.

The question of pets is often difficult, but in general it is safe to say that more harm than good may be done by forbidding them, but they should not be allowed in the child's own room.

CLIMATE AND ASTHMA

A question that is often posed is the possibility of the asthma improving, if the family moves to a different part of the country. The answer is that this is rarely worth while. If it happens that their home is in a low-lying area,

or a wooded valley, and, if they have the opportunity of moving to higher and more open country, then the move may be beneficial. This should not be considered, however, unless both parents welcome the move and unless it has no effect upon the father's income.

Changes in the weather and the fall in the temperature at night are often blamed by parents for the onset of an attack. It is quite likely that physical changes in the air may allow a concentration of dust and pollen that causes an attack, or more directly irritates an already sensitive bronchial tree. A warm, not too dry, atmosphere is therefore probably the best, but the usual tendency on the part of parents is to close the windows and to overheat the child's room. In general it is wisest to encourage open windows and ample ventilation.

It is widely known that children with asthma may benefit from a prolonged holiday in the Swiss mountains and it is often suggested that a child should be sent there. Facilities for this exist, but the disadvantages of this course outweigh the benefit obtained in all but a few carefully selected children. The distance from home, the differences in food, general atmosphere and way of life are liable to cause intense homesickness on the part of the child, and emotional stress on the part of the parents, so that the results are disappointing. In addition, as great a benefit can usually be obtained by a period of convalescence at a suitable home on the English coast. In the case of certain older children, or those whose mother or father can take them, a prolonged holiday in the Alps can be of great benefit, especially as regards general health. The asthmatic attacks themselves are liable to recur soon after return home.

Many asthmatic children respond extremely well to life at a *boarding school*, and several suitable schools are run by local authorities and voluntary associations. The child needs to be eight or nine years of age at least and, whilst the majority do well, the best response comes from those in whom the asthma is largely provoked by emotional stress in the home. A recurrence of symptoms is likely on return home, but these may be transient, and the benefit received by prolonged periods of freedom is generally sufficient to tide the child over a few years. Unfortunately, the tendency is to discharge the child from the local authority schools after a year or less if response has been at all good. The clinging and anxious temperament of the parents of many of the most severe asthmatics generally prevents them from allowing the child to leave them at all.

RESPIRATORY INFECTIONS AND CHRONIC ASTHMA

Respiratory infections certainly seem to play a part in initiating attacks and in causing the persistence of chronic asthma. The story that the attack follows a cold is a common one, although sometimes the 'cold' may be an allergic rhinitis. Attacks often seem more frequent and more severe after an attack of bronchitis or pneumonia, and status asthmaticus is generally associated with some respiratory infection. So far as upper respiratory

infection is concerned, however, the indications for removal of tonsils and adenoids are the same as those for any other child and their removal is unlikely to affect the asthma at all, however much it may improve the child's general condition. The presence of asthma itself is not therefore an indication for the removal of tonsils and adenoids. There may be some value in the prophylactic administration of penicillin or sulphonamides over the winter months in a child with asthma who is also liable to repeated respiratory infection (benzathine penicillin, oral, 300,000 units daily; sulphadimidine or sulphafurazole, 0.5 g. daily).

DRUG THERAPY

Antispasmodics are the main standby and there are advantages in using these prophylactically rather than administering them during an attack. The most useful one is ephedrine: ¼ grain (16 mg.) for children under four years of age—½ grain (30 mg.) for older children. Aminophylline or 'monotheamin' (1½ grain [0.1 g.]), or isoprenaline (10 mg.) tablets. The latter have to be kept under the tongue and are therefore only useful for older children. An atomizer containing isoprenaline solution, 1: 100 (e.g. isoprenaline sulphate spray B.P.C.), is often of value in averting an attack in older children. It does not seem to have the same risk of 'addiction' that an atomizer has for adult asthmatics.

The *antihistamine drugs* have, on the whole, proved disappointing, but are worth trying in individual cases. Promethazine ('phenergan'), 10 mg. daily, or diphenhydramine ('benadryl'), 25 mg. two or three times a day, are sometimes useful, but probably more for their sedative effect than anything else.

Adrenaline (3 to 5 minims [0.2 to 0.3 ml.]) remains the most useful drug in the acute attack; its value is greatly increased by slow subcutaneous injection: 1 minim [0.06 ml.] every one or two minutes.

Sedatives, given over a long period, are of value in those children whose asthma seems to be aggravated and maintained by excessive emotional response on the part of themselves or their parents. Phenobarbitone (¼ to ½ grain [16 to 32 mg.]) once or twice daily, is generally the most useful. 'Franol', a proprietary tablet containing ephedrine, aminophylline and a little phenobarbitone, is very popular.

Cortisone and *corticotrophin* have no place in treatment at present, except in the most severe and intractable asthma and in status asthmaticus.

Status asthmaticus.—It is in the severe prolonged attack that does not respond to adrenaline or any usual measure that death may occur and it is in this condition that ***morphine is most emphatically contraindicated.*** Cortisone or corticotrophin may be life-saving.

PHYSIOTHERAPY

Breathing exercises have been widely advocated and as part of a regime of treatment are certainly useful. They do, however, need the cooperation

of the child and they need to be taught and supervised by an expert. If well taught, the child may learn consciously to relax the chest muscles and even to avert an attack in this way. Well-taught breathing exercises help to some extent in preventing deformity of the chest and faulty habits of breathing even in chronic asthma. A considerable disadvantage is the difficulty in regularly attending a physiotherapy clinic and the rarity of physiotherapists expert in the treatment of children's chests.

ASTHMATIC BRONCHITIS

Asthmatic bronchitis is really a question-begging title which covers more than one condition. It is applied usually to the type of bronchitis which is accompanied by bronchial spasm and wheezing and which is liable to recur frequently in some children. It may be due to asthma; some children, especially before the age of five, who later develop typical asthma, at first present with attacks of coughing accompanied by wheezing. The attacks may be initiated by an infection and there may be some fever. In others there may be an allergic predisposition and perhaps a tendency to allergic rhinitis or hay fever, and consequently any respiratory infection is associated with considerable spasm, but true asthma never develops. Still others are children whose bronchial tree has for some reason become unduly sensitive and reacts to inflammation with an abnormal amount of spasm for perhaps a whole winter or more, but who are not allergic subjects. It causes unnecessary alarm to suggest that the last two groups may be asthmatic.

Clinically the child with this condition has a severe cough, which is dry and irritating, and there is often some fever at the onset. The breath sounds are wheezy and musical rhonchi are present throughout the chest. The course of the disease may be prolonged, but usually the acute symptoms are over in three or four days. Recurrences are common in winter.

Treatment is difficult as the primary infection may respond quickly to antibiotics, but the bronchial spasm, together with the irritating cough, tends to persist, especially at night, preventing the child sleeping and causing particular anxiety to the parents. Apart from the usual measures taken for any kind of bronchitis, a moist atmosphere seems most beneficial and this is sometimes difficult to obtain in modern heated dwellings. Steam inhalations are helpful. Aminophylline, 1½ grains (0.1 g.) by mouth, may relieve the spasm and a codeine linctus relieve the cough. After the acute stage, the bronchitis is likely to respond well to convalescence by the sea or in the mountains, but is certainly exacerbated by the winter fogs of big cities.

HAY FEVER

This condition is fairly common in childhood and is well recognized. The seasonal occurrence of sneezing, nasal discharge, inflamed and irritating conjunctivæ makes the diagnosis obvious enough.

Treatment.—Avoidance of the places and plants which cause the hay

fever is the most successful form of treatment, but this is not always possible. Desensitization to the specific pollens or even to a mixed group is sometimes highly successful and generally ameliorates the symptoms. The injections need to be continued at intervals, or the course repeated for a number of years. Antihistamines are well tolerated by children in the doses recommended by the makers and often give some relief; one of the more recent introductions is chlorpheniramine ('piriton'), 0.2 to 0.4 mg. two or three times daily.

ALLERGIC RHINITIS

This condition is as intractable in childhood as it is in adult life and causes a great deal of minor ill health. It is not usually of any importance before the age of five or six, although symptoms may be present. These consist of persistent or recurrent nasal discharge or, rather more often in children, of a feeling of 'stuffiness' in the nose, and post-nasal catarrh. There may be a slight cough especially on lying down at night. The differential diagnosis lies between allergic rhinitis and chronic upper respiratory infection and obstruction. In allergic rhinitis there is usually a history of allergic rhinitis, or of asthma or hay fever in some other member of the family. The nasal mucous membranes are swollen and a pale pinkish-grey in colour. There is often no evidence of infection, although this may be superimposed. An x-ray of the maxillary antra may show opacity, but more usually thickening of the mucosa only. Skin tests usually show sensitivity to a variety of substances, especially pollens, dusts and moulds.

Treatment is unsatisfactory. Desensitization is less successful than in hay fever and the antihistamine drugs are hardly indicated in such a chronic condition. Avoidance of the causative factors is not as a rule possible. Ephedrine nose-drops are of value during the phases when the rhinitis is most tiresome. Treatment by removal of tonsils and adneoids is not indicated, unless secondary infection has occurred and the condition of these organs is such that their removal is required for the usual reasons. Cauterization, ionization and so on, of the nasal mucosa are not advisable in childhood.

URTICARIA

The typical blotchy urticaria that is seen in adults occurs also in childhood, but more characteristic of this age is the papular or vesicular urticaria that is common in spring and summer and that spoils this time of year for many a child. It is commonest between the ages of five and ten. Intensely itchy, pea-sized red blotches appear on any part of the body, though most commonly on the arms and legs. In the centre of these a vesicle may appear, generally minute but sometimes forming a fairly large bulla. The vesicles are soon scratched off and the child's limbs become covered with sores; these in turn often become secondarily infected. Papular urticaria is most probably a reaction to pollens, especially of grasses. It often follows directly

upon a visit to the park or the country. The urticaria, however, sometimes seems to persist even in the absence of obvious exposure to grasses.

Treatment.—Antihistamines are sometimes very successful in clearing the rash. Local treatment is of little value, apart from antiseptic measures, but, if antihistamines are ineffective, phenobarbitone may help to diminish scratching and loss of sleep due to irritation.

FOOD ALLERGY

Allergy to various articles of food, especially such things as shell fish, occurs in individual children just as it does in adults. Certain children, however, appear to be intolerant to a wider variety of foods including especially eggs, oranges, chocolate and fatty foods, to which they react with vomiting, abdominal pain, diarrhœa and headache. It is improbable, however, that these symptoms are truly allergic. Milk and egg allergy is seen sometimes in small infants, but is a rare phenomenon. It is more often suspected than proved. Milk allergy occurs in the infant of a few weeks or months of age who is put on to feeds of dried or liquid cow's milk. The response to the milk is immediate, with red blotches on the skin of the lips and chin where milk has dropped, vomiting, colic and diarrhœa. The use of breast milk or a soya-bean substitute results in immediate recovery.

Desensitization by the addition of a few drops of cow's milk to the feed and the gradual increase in the amount and concentration over two to three days, the child being fed two-hourly during the day until full feeds of cow's milk are given, often results in a cure. Allergy to eggs can be treated in the same manner. It is sometimes necessary to cover the period of treatment with an antihistamine such as chlorpheniramine (2 mg. twice daily).

ECZEMA

Eczema in infancy is accompanied by an extreme degree of itching and is a most trying disease for both parents and child. It is important therefore to lay stress on the fact that it is self-limiting and that gradual improvement will take place. There are two types. The seborrhœic, in which extreme scurfiness of the scalp is followed by the appearance of small vesicles on the scalp and at the edges of the 'cradle cap', passing down on to the cheeks. The vesicles break down and form greasy flaky scabs over the head and face, and extend down to the shoulders and elsewhere on the body. The other type is the infantile, in which vesicles first appear on the cheeks and then spread to involve most of the face, and appear also in the flexures and behind the ears, eventually tending to clear on the face and remain as a chronic flexural eczema.

The early *diagnosis* is often a problem. A few small scattered papules or even vesicles often appear on the cheeks of babies in the first months of life. The possibility of eczema is sometimes queried by the parents in such cases, and the diagnosis is difficult, especially perhaps when this coincides

with weaning. In general the odds are against the development of eczema, as such a minor rash is very common. On the other hand, the chances are increased if there is a family history of allergy, especially if this is so on both the mother's and father's side. A tendency for the vesicles to break down, weep and scab will confirm the diagnosis of eczema. In the absence of this the application of calamine lotion to the rash, and reassurance of the parents are generally justified, even if there is allergy in the family.

The *etiology* of eczema in infants is uncertain. Infection together with the seborrhœic constitution plays a part in the seborrhœic type and in the infantile type a number of allergens are probably responsible. In some cases it is likely that cow's milk and other foods are at least partly responsible.

TREATMENT OF ECZEMA

The use of a soya-bean milk or a treated milk, such as 'allergilac', may be worth while in very early infantile eczema, but only if the response is obvious. In most cases this is not so and a special diet merely adds another burden to the mother's life. No attempt will be made here to discuss the details of treatment, but the following are a few useful points.

The general family background always needs consideration because of the greatly increased difficulty of treating a child whose parents live in poor circumstances or are not at all intelligent. Allowances need to be made in either case in prescribing a variety of ointments and drugs. As in asthma, so in eczema the strain on the parents may be very considerable, especially if they are losing much sleep, and in these cases the liberal use of sedatives is justified, together with frequent reassurance and encouragement.

In general, infants with eczema tolerate repeated large doses of chloral hydrate (2 to 5 grains [0.12 to 0.3 g.]) and of phenobarbitone ($\frac{1}{4}$ to $\frac{1}{2}$ grain [15 to 30 mg.]). Promethazine, 10 mg. daily, is also helpful.

Bathing in water is rarely harmful and usually advantageous. Sodium chloride, 1 teaspoonful to the pint (0.5 litre), should be added to make the water isotonic; the addition of emulsifying ointment B.P. (15 to 60 g.) to the bath is particularly helpful when the skin is dry. Soap may be used with care, but it should be of good quality.

In the seborrhœic type a few drops of 20 per cent. solution of cetrimide in a pint of warm water is extremely useful in preventing the reappearance of scurf from the scalp, once the worst scabs have been removed.

Eczema is almost always easily cleared by cortisone or corticotrophin, but the result is so transient that their use is not justified other than in exceptional circumstances or in the most severe phases of the disease. Unfortunately once used it is difficult not to continue to use them, but in a condition with a tendency to recur, such as eczema, the risks and secondary effects of cortisone therapy are somewhat too great. Cortisone ointment is equally efficacious, but has similar drawbacks; it is worth using discreetly, however, on severe and persistent lesions which are causing much distress.

THE BLOOD SEDIMENTATION RATE IN CLINICAL PRACTICE

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THAT blood sediments in some illnesses was known to the ancients and is an early example of mistaking cause and effect, since the four layers produced, black bile (melancholia), sanguis, phlegma, and yellow bile, were accredited with being the cause of ill health. A similar concept, persisting until quite recent times, was the rationale of venesection, which was intended to remove the noxious crusta inflammatoria (fibrin and leucocytes). It was not until 1921, however, that the blood sedimentation rate (B.S.R.) as we know it, arrived; its pioneer was Fahræus. Since that time the phenomenon has excited much investigation, whose review is outside the scope of a short article.

MECHANISM

The sedimentation of blood to which an anticoagulant has been added is a complex process. Basically it obeys the physical law which relates the velocity of fall of a particle through a fluid to the diameter, volume, and density of the particle, and the specific gravity and viscosity of the fluid. In the case of blood the rate of sedimentation of the cells is proportional to the degree of rouleaux formation, and this is influenced mainly by the plasma proteins, especially those with highly asymmetrical molecules such as fibrinogen. The larger the rouleaux produced, the greater is their weight relative to their surface area, and hence the greater their velocity of fall. In addition to plasma proteins, other substances—cholesterol, large molecule polysaccharides such as dextran, and perhaps muco-proteins—will hasten the sedimentation rate. The rate is also affected by the number and size of the red cells and by the charges which they carry.

Expressed in simple terms, however, the B.S.R. is a measure of quantitative change in the protein constituents of plasma, being increased by fibrinogen and the other globulins, and being retarded by albumin. It is often stated that fibrinogen has a far greater effect than the other globulins, and this is true enough. Weight for weight, fibrinogen is about eight times as potent as electrophoretically pure gamma globulin (Fearnley, 1950), but it must be remembered that there is about eight times as much globulin present in plasma as there is fibrinogen and that changes in disease are of the same order. The very high B.S.R. of myelomatosis, for example, is mainly due to the high globulin level found in this disease.

METHODS

Unfortunately, a number of different methods of measuring the B.S.R. has been developed, all of which are in current use. Since the anti-

coagulant, and width and length of tube, vary, readings with one method are not comparable with those of another. The universal adoption of one method would be desirable, and the Westergren seems to me to be the

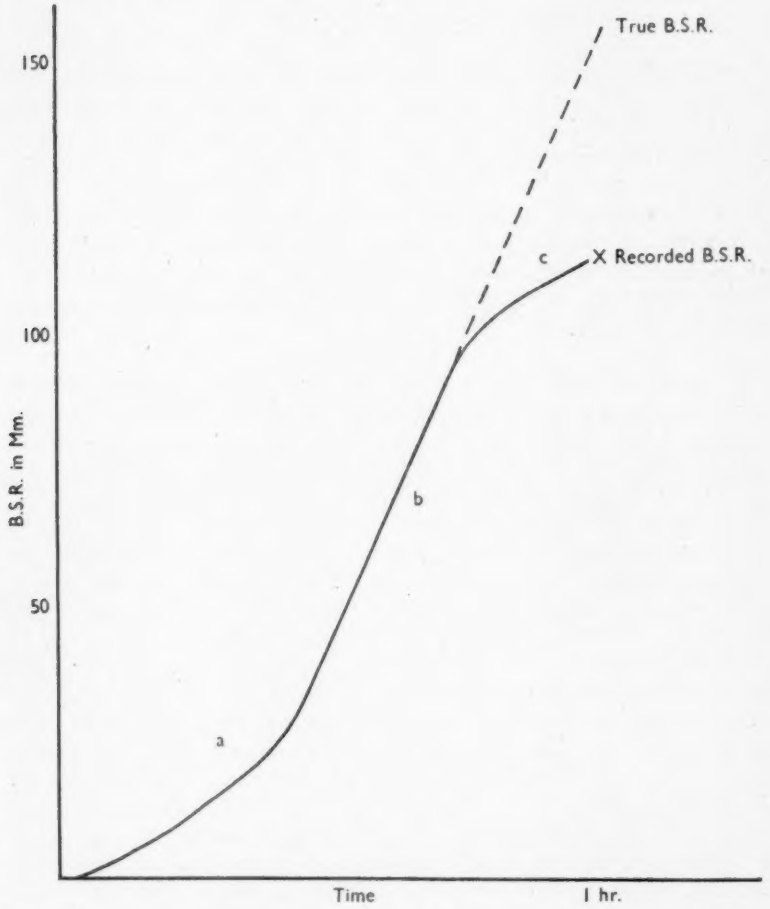

FIG. 1.—Curve to show the kinetics of the blood sedimentation rate when readings are taken every two minutes and plotted against time.
a = Period of rouleaux formation.
b = Period of constant fall.
c = Period of packing.
The true B.S.R. at one hour can be obtained by extrapolation, as shown by the dotted line.

method of choice. This is not a laboratory procedure, as is the full Wintrobe method; it can be done easily in the surgery, outpatient department and

ward. The test is most simply performed as follows:—

Two millilitres of venous blood obtained in a syringe are added to 0.5 ml. of 3.8 per cent. sodium citrate solution (measured out with a 1-ml. syringe) in a small gallipot or universal container. The Westergren tube is filled to the zero mark by suction and the tube set up in the stand. The B.S.R. is read after one hour. It is necessary to ensure that the tube is vertical, since even a 10° slope will produce a significant acceleration of the rate. Furthermore, since the sedimentation rate increases with temperature, close proximity of the tube to a radiator or other source of heat should be avoided.

Normal readings.—The usual figures given for one hour are: men: 3 to 5 mm.; women: 4 to 7 mm. These figures are too low: 15 mm. should be taken as the upper limit of normal.

The superiority of the Westergren method.—It is necessary to consider briefly the kinetics of blood sedimentation in a tube. If readings taken at frequent intervals are plotted against time, a sigmoid curve is obtained (fig. 1). The first or accelerating part of the curve is due to rouleaux formation; the second part is the period of constant fall; and the third, or decelerating, part of the curve is the period of 'packing', i.e. the fall is mechanically impeded by the increasing density of the red cell mass, and eventually ceases. It is obvious that the faster the sedimentation rate, the earlier within the hour will the effect of packing occur. With fast rates the reading obtained will therefore be affected by the length of the tube. Admittedly, by taking frequent readings as illustrated, the true B.S.R. at one hour can be obtained by extrapolation, or the fall per minute can be calculated from the period of constant fall (Rourke-Ernstene method, 1936), but this is too time-consuming for routine use.

In the interests of accuracy therefore the longer the tube the better; and the Westergren tube of 200 mm. is the longest tube of practical size in use. With the shorter tubes (e.g. Wintrobe, Cutler) the effect of packing will occur earlier.

THE VALUE OF THE B.S.R.

Although there seems to be a rather widespread belief that a raised B.S.R. is diagnostic of tuberculosis or the inflammatory rheumatic diseases, it is not so. Conversely, one meets the view that since the B.S.R. is raised in so many conditions, it is of no value. The same criticism could be applied to the temperature, but one has yet to hear of the doctor who has discarded his clinical thermometer for this reason. The value of the B.S.R. can be summarized as follows:—

(1) A raised B.S.R. in a patient in whom clinical and other examinations are negative almost invariably means organic disease.

(2) A raised B.S.R., in addition to the history and clinical findings, may strongly favour one of a number of possible diagnoses.

(3) The B.S.R. is a sensitive indicator of progress or otherwise in tuberculosis, rheumatic fever, rheumatoid arthritis, and many other conditions.

In brief, a raised B.S.R. means organic disease, and in some circumstances may be a diagnostic pointer.

THE NORMAL B.S.R.

The B.S.R. of the male is remarkably constant for the individual in health, normal values being 2 mm. to 12 mm. per hour, when done by the Westergren method. The female B.S.R. increases slightly with menstruation (about 5 to 10 mm. increase) and markedly with pregnancy; from the fourth month of pregnancy onwards, the Westergren B.S.R. may be raised to as much as 40 to 50 mm. per hour. Young, fat, adolescent girls have been stated to show moderately elevated B.S.R.s, but I have not personally encountered this. In rheumatism clinics, where the B.S.R. is usually done as a routine test on all patients, a few patients are found to have moderately or even greatly elevated B.S.R.s for no apparent reason. Follow-up or further investigation of such patients will bring to light in some a deep-seated malignant growth or other disease, but there will remain a few people who continue to enjoy good health, in spite of a pathological B.S.R. It must be emphasized that such patients are very uncommon. Finally, in the very old a moderate but not a great elevation of the B.S.R. may be found in the absence of definitive disease. Apart from these exceptions a raised B.S.R. means inflammatory or malignant disease.

RESPIRATORY SYSTEM

Upper respiratory tract.—Although many textbooks state that catarrhal inflammation of the upper respiratory passages does not affect the B.S.R., in my experience this is untrue. A simple coryza may produce an increase of 10 to 15 mm. in the Westergren B.S.R. The practical importance of this is that when a patient is found to have an unexpected, slight elevation of the B.S.R. the possibility of coryza should be looked into, and the test repeated later. Pus under tension in a nasal sinus, a quinsy, or a dental abscess will give a considerable elevation of the B.S.R.

Lower respiratory tract.—In chronic bronchitis the B.S.R. is not elevated but goes up during an exacerbation. All pneumonias are accompanied by a raised B.S.R., acute lobar pneumonia having the greatest effect and primary atypical pneumonia the least. Bronchiectasis and lung abscess raise the B.S.R., as do the granulomas, tuberculosis and actinomycosis. In uncomplicated pneumoconiosis the B.S.R. is normal, an elevation together with massive nodular fibrosis suggesting a superadded tuberculosis. Malignant pulmonary neoplasms, both primary and secondary, usually raise the B.S.R. (In this connexion, it must be stated that, whereas a malignant neoplasm anywhere in the body is commonly accompanied by a raised B.S.R., this is not invariable, and a normal B.S.R. does not exclude malignancy.)

Pleura.—The B.S.R. is raised in dry and wet pleurisy and in empyema.

GASTRO-INTESTINAL SYSTEM

Stomach.—Peptic ulcer does not raise the B.S.R. A high B.S.R. in a patient with a large ulcer of the stomach is in favour of malignancy.

Intestines.—Neoplasms and inflammatory conditions, dysenteries and ulcerative colitis, raise the B.S.R. Acute appendicitis is apparently an exception, the B.S.R. remaining normal for the first twenty-four hours.

Gall-bladder.—Acute cholecystitis and empyema of the gall-bladder, but not simple gall-stone colic, are accompanied by a raised B.S.R.

Liver.—The B.S.R. is raised in metastatic and many inflammatory liver conditions. Its behaviour in hepatitis and cirrhosis is, in my experience, variable. When, as often occurs, the plasma globulin is raised and the albumin diminished, the B.S.R. is found to be raised.

Pancreas and spleen.—Acute pancreatitis and splenic infarction raise the B.S.R.

RENAL TRACT

Acute nephritis, pyelitis, exacerbation of a chronic pyelonephritis, and neoplasm of the kidney cause a raised B.S.R. The renal condition, however, in which a very high B.S.R. is commonly found is 'nephrotic nephritis'. Here the low plasma albumin, high globulin, and raised cholesterol levels all contribute to the elevation. Inflammatory conditions of the lower urinary tract produce variable elevation of the B.S.R., depending upon the degree of inflammation and tissue destruction.

FEMALE GENITAL SYSTEM

Inflammations and malignant neoplasms raise the B.S.R., whereas benign conditions, such as fibromyomas and ovarian cysts, do not.

CARDIOVASCULAR SYSTEM

The effect of various cardiac conditions on the B.S.R. must be reviewed in the light of the reduction in level produced by cardiac failure. For example, if a patient with active rheumatic carditis and a high B.S.R. goes into congestive failure, the B.S.R. is likely to fall sharply, presumably because the congested liver fails to keep up the level of circulating fibrinogen. A falling B.S.R. in these circumstances is, of course, no indication of improvement. The advent of congestive failure has exactly the same effect on an elevated B.S.R. due to any other cardiac condition.

Coronary thrombosis.—Following an infarct, especially a large one, the B.S.R. begins to rise on the fourth day and remains elevated for a further ten days to two weeks. If the electrocardiogram is inconclusive or unavailable, a rising B.S.R. is of great confirmatory value.

Subacute bacterial endocarditis.—An elevated B.S.R. is the rule, and should raise suspicion of this diagnosis in an outpatient with a long-standing valvular lesion who complains of recent ill health, but whose temperature record is lacking.

Aortic aneurysm and syphilitic aortitis.—A raised B.S.R. is often said to be of diagnostic value in aortic incompetence due to syphilis. As a guide to satisfactory treatment, it is helpful, but it is scarcely diagnostic as aortic incompetence due to rheumatism may be accompanied by active carditis.

Pericarditis.—Rheumatic, 'acute benign', tuberculous, and suppurative pericarditis all cause an elevation of the B.S.R.

CENTRAL NERVOUS SYSTEM

Infective and neoplastic conditions of the central nervous system in general cause an elevated B.S.R. Poliomyelitis is an exception.

MUSCULOSKELETAL SYSTEM

Rheumatic fever.—A raised B.S.R. is almost invariable and, as is well known, is a useful guide to progress, particularly when the heart is involved. (I have, however, seen one patient in whom carditis developed in spite of a B.S.R. never greater than 5 mm./hour on repeated testing. This must be rare.)

Rheumatoid arthritis.—In all but about 10 per cent. of patients with active rheumatoid arthritis, the B.S.R. is elevated, the level depending in part upon the severity and extent of joint involvement. The practitioner, however, should be prepared to diagnose rheumatoid arthritis when other evidence is present, even though the B.S.R. is not raised. Conversely, a few patients who complain of vague joint pains but whose joints are objectively normal will be found to have a raised B.S.R. Such patients in the course of time often develop rheumatoid arthritis.

Osteoarthritis.—The B.S.R. is not raised.

Gout.—The B.S.R. rises to high levels during an acute attack and subsides as the patient recovers.

'Fibrositis' and non-articular rheumatism.—The B.S.R. is normal.

Collagen diseases.—The diffuse collagen diseases are all accompanied by a raised B.S.R.

Ankylosing spondylitis.—A raised B.S.R. is of less value as a guide to activity in this condition than in rheumatoid arthritis. The B.S.R. in some patients is greatly raised, but in others only a moderate elevation or no elevation at all is found, in spite of progressive limitation and disability.

Bone diseases.—Primary and secondary malignant growths and inflammations, pyogenic, tuberculous, and syphilitic, raise the B.S.R. The bone disease in which an abnormally high B.S.R. (over 100 mm./hour) is classically found is myelomatosis, a normal B.S.R. making this diagnosis unlikely.

HÆMOPOIETIC SYSTEM

The reticuloses.—The B.S.R. is raised in the malignant reticuloses and also in the leukæmias, both acute and chronic.

Anæmia.—The effect of anæmia must be examined in some detail. That anæmia *always* raises the B.S.R. is generally believed; that it *may* raise the B.S.R. is more correct. The Wintrobe correction (Wintrobe and Landsberg, 1935) is widely known and used; its desirability is questionable and its validity dubious. In rheumatoid arthritis and rheumatic fever, anæmia is one of the indications of activity and to correct one indicator by trying to

exclude the effect of another seems to be academic and misleading. There are, however, more serious objections than this to Wintrobe's correction. In the first place, as emphasized by Terry (1950), anæmia by no means invariably raises the B.S.R.; in fact microcytic anæmia often actually retards it. Given a patient with anæmia and a raised B.S.R., it is quite impossible by guesswork to determine what part the anæmia is playing, and this renders attempts at correction invalid. Such attempts might be feasible if we had precise information on the effects of various types of anæmia; but Wintrobe's correction ignores the complex variables of abnormal blood and plasma, and cannot therefore be recommended.

OTHER CONDITIONS

In addition to all of the above conditions, where the test may be of diagnostic or progress value, the B.S.R. tends to be elevated in infections and toxæmias, after operations and fractures, and after irradiation.

EXAMPLES

A few examples are now given to show the practical value of the B.S.R.

(1) A nurse was admitted to hospital with a diagnosis of erythema multiforme. Put on penicillin by the resident staff, her temperature and skin lesions subsided quickly and she was allowed to go home. An apparently symptomless mitral stenosis, however, was noted. When seen at outpatients two weeks later she did not look well, although she had no complaints. The B.S.R. was 80 mm./hour. Further admission resulted in a diagnosis of bacterial endocarditis, for which she was successfully treated.

(2) A young woman of neurotic disposition complained of vague joint pains. Clinical examination was negative. On obtaining a B.S.R. of 32 mm./hour a diagnosis of functional joint pains was changed to early rheumatoid arthritis, of which she subsequently developed objective evidence.

(3) A middle-aged man was seen who complained of headache and depression of recent onset. Clinical examination revealed no cause. A B.S.R. of 65 mm./hour suggested malignancy, and further investigation revealed a small symptomless bronchial carcinoma with metastases to the brain.

(4) An elderly man complained of backache of six months' duration. An x-ray of the spine revealed a diffuse osteoporosis. The B.S.R. was 140 mm./hour and this suggested myelomatosis of the osteoporotic type, which was confirmed.

SUMMARY

(1) The value of the B.S.R. as a simple test for the presence of organic disease is described.

(2) The behaviour of the B.S.R. in disease of the various systems is reviewed.

(3) A plea is made for the universal adoption of one method, the Westergren; and reasons are given why corrections for anæmia are undesirable.

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WASP AND BEE STINGS

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Stinging by bees and wasps is a common occurrence and the effects are usually of little consequence. A severe systemic reaction occasionally results but a fatal outcome is sufficiently rare to be outside the first-hand experience of most practitioners. Reports in the medical literature are infrequent and the subject is ignored by the textbooks of medicine. The reports available are chiefly concerned with bee stings; death by wasp sting was last reported in a British journal in 1941[25]. It seems timely therefore to report a case of sudden death following wasp stings and to review the literature concerning reactions to the stings of bees and wasps.

CASE REPORT

A.B., a man of 52 years, had always enjoyed good health. On the evening of August 11, he was working with his wife in his allotment which adjoined a railway, and having occasion to visit a smaller allotment on the far side of the embankment, he was out of her view for fifteen to twenty minutes. He returned at about 6.25 p.m. and said, laughingly, that he had put his fork into a wasps' nest while digging, and that he had been stung on the back of the neck, on the right arm, and on the right side of his chest through his clothing. He was perspiring but this was not unusual; otherwise he appeared to be quite normal.

Almost at once he became pale and he sat down at the entrance to a garden hut while his wife bathed his stings. They appeared as white rings about 1/5th of an inch (5 mm.) in diameter, with a red spot in the centre. Asked if he felt faint, he replied 'Yes', and was told to put his head down between his knees. He then began to look 'ghastly'. His wife went for water from a nearby brook and bathed his head. From this time onwards he did not speak; his arms hung limply by his sides and his ears turned blue. His wife thought he was going to be sick and she took out his false teeth but he did not vomit; he made only some faint gurgling sounds. He went unconscious but his wife continued to hold him in a sitting position and shouted for help. When two men arrived on the scene he was still breathing but this stopped a few minutes later, at about 6.40 p.m. A doctor arrived soon afterwards and confirmed that he was dead.

Principal necropsy findings.—The body of a well-nourished, middle-aged man. On the front of the chest overlying the second right rib there was a red macule, 3/16 of an inch (5 mm.) in diameter, which had a pale centre. No other sting marks could be found.

Conjunctivæ: About two dozen petechial hæmorrhages were seen in each lower lid.

Pharynx: Slight œdema of the uvula.

Trachea: The mucosa was congested.

Bronchi: Both main bronchi contained mucus and some regurgitated food. The smaller bronchi contained mucus.

Heart: 13½ ounces (380 g.). There was atheroma of patchy distribution of the coronary arteries, most severe in the first inch of the descending branch of the left where the lumen was severely narrowed. The valves and the heart muscle were healthy. Subendocardial hæmorrhage was present over the upper half of the septal wall of the left ventricle and the adjacent part of the posterior wall.

Lungs: Emphysematous. They were pale in colour. Slightly depressed, dark red areas of collapse were scattered over their lateral surfaces.

The cause of death was allergic shock following wasp stings. Inquiry into the patient's history revealed no allergic tendencies or knowledge of previous stinging by bees or wasps.

THE INCIDENCE OF HYPERSENSITIVITY

In most cases, a sting by a bee or a wasp causes only a local reaction characterized by pain, redness and slight swelling at the site. Toxic systemic effects due to the venom itself do not occur until many stings are received coincidentally.

Bee-keepers know that repeated stinging over a period of time produces an immunity in about 75 per cent. of individuals; the actual prick remains painful but the local reaction is transient. About 10 per cent. of persons are immune from birth; 15 per cent. never develop immunity but continue to react locally. Acquired immunity is not permanent; it disappears in a few months if fresh stings are not received.

In about 2 per cent. of persons[106], repeated stinging creates a state of hypersensitivity in which each fresh sting produces reactions of increasing severity. In some persons there is only an intensification of the customary local reaction, but in others the reaction is generalized in character, producing alarming symptoms akin to those of anaphylactic shock; in a few of these persons the final sting results in death. Some develop hypersensitivity after their first sting[13, 72, 97], but in others it arises after a series of normal reactions[14, 18, 20, 30, 53], or even after some degree of immunity has been acquired[3, 87]. In a few, hypersensitivity appears to be inborn; their first known sting results in death.

Reactions to the sting of a wasp appear to differ little from those of bees. The only significant difference is infection. Unlike bees, wasps and hornets are scavengers and likely to transmit infection along with their venom.

THE STINGING MECHANISM

Many female insects possess an ovipositor—an organ used for depositing their eggs. In the bee, wasp and ant the ovipositor has lost its original function and become a stinging apparatus. The males of the species are stingless.

The bee.—The sting of the bee[15, 16, 49, 99], which is about 2.5 mm. in length, lies hidden inside a cavity at the tip of the abdomen from which it is extruded when about to attack. It is a hollow needle split longitudinally into three pieces which together surround the poison canal. The dorsal segment, the director, bears ridges along which the two ventral segments, the lancets, slide up and down by muscular action. The tips of the director and these lancets are barbed. The poison canal has a bulbous enlargement at its abdominal end which communicates with a poison sac. The two lancets terminate within this bulb as lobe-like structures which, in the process of stinging, serve as plungers to force the venom down the poison canal. The venom glands, which lie under the last few abdominal segments, consist of a pair of acid-secreting glands, large tubular structures composed of polyhedral cells, and a much smaller alkaline gland. The secretion of the acid glands is poured into the poison sac either separately or by means of a common duct; that of the alkaline gland is discharged into the poison canal where it is mixed with the acid component just before injection into the victim.

When the sting penetrates the skin, the two lancets, working alternately, slide backwards and forwards along their tracks; with each thrust the barbs anchor the lancets deeper and deeper in the flesh. The same movement also operates the plungers on the lancets which expel the venom.

The stinging of one bee by another is no more than a rapid thrust of the sting into a vulnerable area and its immediate withdrawal. When the sting pierces human skin, however, the lancets are so firmly anchored by their barbs that they cannot be withdrawn; when the bee struggles to escape or is brushed off it is usual for the whole of the stinging mechanism to be avulsed from the bee's body. Damaged in this way, the bee soon dies. Reflex action of the muscles still attached to the lancets continues to drive them, by their pricking movements, deeper into the flesh of the victim and at the same time more venom is driven out of the poison sac.

The wasp.—The stinging mechanism of the wasp[23, 40, 49] does not differ fundamentally from that of the bee. The sting itself is larger and semi-cylindrical in shape. The lancets are not barbed and consequently the wasp can easily withdraw its sting when it escapes; it is therefore unusual to find a wasp sting embedded in the skin. The lancets do not bear plungers; the venom is expressed by the contraction of a strong muscular layer which invests the poison sac[40].

THE VENOM

The venom of the *bee* is a clear colourless fluid. It is formed in the poison canal of the sting by a mixing of the secretions of the 'alkaline' and 'acid' glands, neither secretion being toxic of itself[89]. Each bee yields about 1/10 to 1/3 mg. of venom[31, 89, 93].

Its chemical composition has been studied by different observers for over 100 years and the results are still inconclusive. Langer[62] was the first to show that formic acid, once thought to be the active principle, was not a constituent. Flury[31] isolated a non-nitrogenous substance which is related in its action to the saponins, the active principle of snake poisons. Histamine was shown to be a constituent by Marcou and Derevici[69]. Reinert isolated 10 mg. of histamine from 1 g. of crude venom[29].

In its physiological action bee venom has for long occupied a place intermediate between the sapotoxins and cantharidins. The similarity between the venoms of the bee and viper was pointed out by Lyssy[67]. Its similarity to cobra venom was reported by Feldberg and Kellaway[28], and Essex, Markowitz and Mann[27] found its effects to be similar to those of rattlesnake venom, particularly in its hæmolytic action; if sufficient stings are received at the same time the clinical picture resembles that of rattlesnake poisoning.

Electrophoresis, paper chromatography, and the electron microscope have thrown further light on this problem and the results have been reviewed by Hodgson[47]. It is now known that bee venom contains a number of basic and acid components of which two principal ones, designated F_1 and F_2, are basic. F_1 contains a hitherto unknown, yet pharmacologically active, protein which has been termed 'melittin'. This fraction contains the hæmolytic factor of the venom and also causes general and local effects. F_2 contains the most powerful dehydrogenase inhibitor known, more powerful even than that of cobra venom, and a hyaluronidase which may assist permeation of the venom.

The venom has been shown to have four characteristic toxic effects:—

(1) A *hæmolytic effect* which resembles that of the sapotoxins. This accounts for such symptoms as hæmoglobinuria[59].

Bee venom is hæmolytic in a concentration of 1 : 1000[55] and hæmolysis is preceded by an increase in the red cell volume[27]. The factor responsible, which is not destroyed by acid hydrolysis[56], has been separated by electrophoresis into two components[78]: one a lecithinase which transforms lecithin into hæmolytic lysolecithin and another which has a direct hæmolytic action. Their action *in vitro* is inhibited by a calcium ion concentration in excess of normal[96] and heating at 90° C. for thirty minutes inactivates the venom[64].

(2) A *hæmorrhagic effect* which is responsible for the uterine bleeding[70, 103], and melæna[6, 85] which sometimes follow stinging. It has been found by experiment that bee venom raises the coagulation time of the blood either by preventing the formation of thrombokinase or by interfering with its action[5, 24, 77].

(3) A *neurotoxic effect* which causes, in some species, extensive paralysis and death. It is destroyed by acid hydrolysis[56].

(4) A *histamine effect*.—Histamine is probably formed in the acid gland, because it is destroyed in an alkaline medium[69]. Not only is histamine an active principle of the venom but it also causes the release of more histamine from the body tissues[28, 29]. The histamine in the venom and that released in the tissues are together responsible for the triple response—the redness, flare and weal—seen in the skin.

Little is known about *wasp* venom; only in the last few years has any experimental work been done on it[52]. Like bee venom it contains histamine but its concentration, 16 to 20 mg. per g. of dried venom, is about three times greater. It also contains 5-hydroxytryptamine, a hyaluronidase, and a substance which resembles bradykinin, the slow-contracting substance obtained by incubating globulin with snake venom.

THE LOCAL REACTION

At the time that a bee sting pierces the skin, there is a sharp prick followed by pain which lasts for a few minutes. The degree of pain experienced is usually slight but can be severe. Within a few minutes a small red area appears at the site of the sting and this becomes surrounded in turn by a whitish zone and a reddish flare. A weal then forms and, as this subsides in a few hours, it gives place to irritation, itching or a feeling of heat. All trace of the sting usually disappears within twenty-four hours. The reaction is a direct outcome of the injection of venom and can be accounted for by its content of histamine augmented by that released in the tissues. Histamine is also partly responsible for the initial pain associated with stinging[4].

If the sting is received in the mouth or the throat, the local reaction in the tongue or loose connective tissues may produce an œdematous swelling of such severity that the airway is obstructed and a tracheotomy becomes imperative to save life[1]. Death has resulted when this treatment has been delayed[82].

Laryngeal and pharyngeal œdema has also arisen from a sting on the side of the face[32, 98], on the neck or on a distant part of the body[88, 103, 104]. Œdema of these areas is a frequent finding, and is likely to be as severe when the sting is on a limb as when on the head and neck. The œdema is not a local phenomenon as is sometimes suggested[40] but part of the general reaction.

Infection introduced by a wasp sting may cause cellulitis to develop some hours or days after the sting.

A man, aged 56, developed severe constitutional symptoms and lymphangitis of the forearm after a wasp sting on the finger[104]. Leadman[63] recorded the death of a young man from acute cellulitis of the cheeks, jaw and neck, nine days after he had been stung by a wasp on the right side of the neck. A woman died from septicæmia and cellulitis of the throat eight days after being stung in the throat by a wasp[72]. Mease[71] tells of a man who died twenty-seven hours after a wasp sting to the left side of the throat. A tracheotomy had been performed at the urgent request of the patient and it would appear that the swelling of the throat was due to infection rather than to any hypersensitive reaction.

THE TOXIC REACTION

If, as sometimes happens, a person is attacked by a swarm of bees he may receive sufficient venom to cause systemic poisoning. Poisoning in this manner has followed 300 to 400 coincident stings and when the stings exceed 500 death may result.

An instance of a systemic reaction to a high dose of bee venom is reported by Koszalka[59]. A young man was attacked by thousands of bees and over 600 stings had to be extracted. In his fright, pain and exhaustion he lost consciousness soon after being stung and when he came round he was violently sick and incontinent of urine and fæces. When found, he was acutely ill, weak and exhausted. There was severe inflammatory œdema of the head and neck, tongue, hands and wrists and this increased in severity until the lips, eyelids, nose and ears were enlarged three times. He could not then open his eyes and was barely able to speak or swallow. His urine was red-brown in colour and the hæmoglobinuria lasted for about thirty-six hours. He improved gradually with treatment except for an urticarial attack on the 5th to 6th day.

The clinical findings in these cases resemble those of hypersensitive reactions, except for the greater frequency of gastro-intestinal upsets. The principal symptoms—diarrhœa, vomiting, faintness and unconsciousness—were present in three cases reported by Jex-Blake[53]. Beven[12], who treated two severe cases, reported vomiting, abdominal cramps and respiratory difficulty; one had diarrhœa and the other became comatose. Recovery from the severe effects usually takes place within twenty-four hours but an urticarial attack may follow at the end of a week.

Reports of multiple wasp stings are uncommon and they lack detail.

Heilbronn[43] treated a man suffering from about 1000 stings after he had disturbed a wasps' nest. He was shocked and cyanosed; his lower lip was greatly swollen and he had a generalized urticaria. Heilbronn[44] also reported an instance of suicide by hornet stings. A man undressed himself and sprang into a hornet's nest where he sat for ten minutes until the fire-brigade scattered the hornets with smoke.

THE ANAPHYLACTIC REACTION

Generalized reactions occurring after a few stings or even a single sting,

although uncommon, are of importance since they are associated with alarming symptoms of allergic shock which sometimes, as in the present report, is fatal.

The symptoms arise within twenty minutes and in many cases they follow immediately on the sting. Their intensity usually reaches a maximum within thirty minutes and the victim may suffer acutely for an hour or so. The reaction then abates and, apart from mild residual symptoms, recovery takes place within three to four hours. The main symptoms can be related to the action of histamine on the smooth muscle of susceptible areas of the body and to its action in increasing vascular permeability. The most constant symptoms are respiratory distress, faintness with partial or complete loss of consciousness, followed by some form of rash which may itch.

Some persons experience flushing of the skin[13, 25, 84, 109] but others who exhibit peripheral circulatory shock become pale[3, 36, 41, 48] and those who have dyspnœa may become cyanosed[45, 73, 79, 83, 110]. Swelling of the face is common even though the sting is on a limb[22, 36, 41, 65, 68, 81, 84, 88, 109] and swelling of the pharyngeal region may constitute a danger to life.

At least a third of the patients have nausea or vomiting and this may be accompanied by abdominal pain[6, 17, 87] or cramps[81, 98] or diarrhœa[39, 41, 98, 104]. The abdominal pain in women may simulate the pains of labour[13, 33, 70]. Urinary incontinence[53, 65] is not necessarily associated with unconsciousness. Sweating is pronounced in about 10 per cent. of persons[3, 41, 53, 71, 109, 111], and about the same proportion have rigors[39, 41, 53, 104].

Other symptoms are infrequent. Pyrexia occurred in only two cases[39, 41], sneezing in one[73], salivation in one[60] and lacrimation in three[22, 71, 83]. Ross[98] reported peripheral neuritis after a honey-bee sting and Sonck[100] a disseminated papular rash resembling that of secondary syphilis following the sting of a wasp.

Only rarely[75] has there been comment on the fact that some persons after recovering from their initial attack develop urticaria at about the seventh day. In these cases[12, 59, 90] it is probable that a large dose of venom is received by a person who is not sensitized; the mechanism is comparable to the antigen-antibody reaction which causes serum sickness.

In fatal cases, death usually occurs within fifteen to twenty minutes after the sting[2, 35, 46, 105]; it has been reported as early as two minutes[53]. The present case is an example of the sequence of events. The symptoms are due to profound vasomotor collapse, which also explains the slight local reaction often remarked upon in the reports. When death results it may be impossible to find the site of the sting at necropsy; in the present case only one of three stings could be identified.

Although it is now generally accepted that stinging can cause death, there was a time when these accidents were attributed to other causes[61]. When it was acknowledged that stinging was responsible it was at first believed to be a toxic death. Some[7, 35, 32, 60, 92, 94] believed that those who died had received a dose of venom intravenously. The symptoms were then recognized as allergic and Waterhouse[109] suggested that the reactions might be due to sensitization by previous stings. As late as 1928, however, Gibb[34] described an attack resembling hay fever in a girl of 7 years following a bee sting and erroneously attributed the symptoms to allergy to pollen adherent to the bee's body or injected with the venom.

Benson and Semenov[11] found that the hypersensitivity was to a water-soluble, protein fraction derived from the bee's body; the sting caused sensitization only because this allergen was included in the poison. A reaction to a bee sting is therefore a manifestation of hypersensitivity to bee protein and not to the venom *per se*. Hypersensitivity is in many cases an acquired state and sensitivity increases with consecutive stings. Sensitization becomes established in a matter of days. The development of sensitivity to wasp stings within an hour[48] must be discounted; other factors must have been involved.

Although the antigen is usually injected with the sting there are a few persons who are sensitive to bee antigen dispersed in the air[26, 30, 70]. They react with symptoms of hay fever whenever they come near to hives, frames and the clothing of bee-keepers. Symptoms may arise soon after contact with the airborne allergen, or not until some hours after exposure.

THE NATURE OF SENSITIVITY TO STINGS

The specific nature of this sensitivity in many cases cannot be doubted; each succeeding reaction is worse than the preceding one[8, 13, 30, 42, 51, 53, 98]. Sometimes the sensitivity is highly specific but in other cases[91] antigens of a less specific nature are involved, for once the subject is sensitized symptoms are evoked indiscriminately by bees, wasps or ants.

There are, nevertheless, many cases on record in which, as in the present case, symptoms have occurred after what is believed to have been the first sting. It is, of course, impossible to be certain that the person had never previously been stung, yet these reports are not lightly to be dismissed. It is conceivable that some persons have an inherited sensitivity and the sting acts as a trigger mechanism. It is well known that persons who display symptoms of allergy when exposed to certain foods or pollens may react violently to a first injection of foreign protein, and it may well be that such individuals experience allergic symptoms following their first sting.

There is no doubt that many factors yet unrecognized play a part in determining reactions to a sting. Hypersensitivity may suddenly develop in those previously immune, e.g. experienced bee-keepers. Such an event is common enough but the mechanism is unknown.

DESENSITIZATION

Successful desensitization of subjects hypersensitive to bees supports the allergic basis of these reactions.

One of the earliest reports is that of Braun[13] who desensitized a girl by inoculation with increasing doses of an extract prepared from the posterior segments of bees' bodies. Gregg[39] mentions successful desensitization of a boy by submitting him to a graduated number of bee stings throughout a year.

Benson and Semenov[11] concluded their investigations by desensitizing their original patient. Fisher[30] reported a distinct lowering of sensitivity to bee stings following a course of injections of whole bee extract. More recently, Ward[100] used bee venom, Prince and Secrest[91] and Pepys[87] used whole bee extract and Mueller and Hill[76] used bee and wasp extracts singly and admixed. McLane[70], who used

whole bee extract for the major part of the treatment, used actual bee stings for the later stages and for maintenance therapy.

Bee venom is supplied by Antibody Products Ltd. in their skin test sets for allergy and in treatment sets for desensitization.

The course of treatment they recommend is that of Ward[108]. The venom is prepared in two strengths, 5 units per ml. with 1/6000 adrenaline, and 120 units per ml. without adrenaline; ten units are equivalent to one average sting. Treatment starts with a subcutaneous dose of 0.1 ml. of the weak solution and injections are continued every other day, doubling the dose each time. After the fifth injection (1.6 ml., equivalent to 8 units), treatment is continued with the stronger solution, the doses being 0.1, 0.15, 0.225, 0.34, 0.5, 0.75, 1.15 ml., when it is claimed that immunity should then be established.

Others have worked with an antigen consisting of an aqueous or isotonic saline extract of whole bee bodies.

Methods for its preparation are described in the *Journal of the American Medical Association*, 1948[50], and by Mohammed[74]. Dilutions down to 1:1,000,000 are prepared. The patient is tested with 0.02 ml. of the weakest solution and note is taken of the reactions at twenty minutes and twenty-four hours. If neither of these reactions is significant, the patient is tested on the following day with the next dilution, and the procedure is continued until one of the reactions is notable. Desensitization is begun by using 0.05 ml. of that dilution which first produced a significant reaction, i.e. weal or erythema. On succeeding alternate days the dose of this extract is raised thus:—0.05, 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1 ml. The same procedure is then repeated with the next stronger extract. The maximum dosage varies from person to person; some tolerate even the 1:10 dilution.

Wasp venom is not produced commercially but a satisfactory extract can be made in the laboratory by the methods referred to. The technique of desensitization is similar to that for bees.

Great care must be taken not to produce a severe reaction and adrenaline must be at hand for use in an emergency. Provided all precautionary measures are taken, the risk of a severe reaction and fatal shock is relatively small[95]. Nevertheless, in patients who are unduly sensitive it may be wise to give further protection; the risk can be reduced to negligible proportions by the administration of cortisone by mouth, daily, during the period of treatment.

In some cases desensitization will be complete and permanent. In others, particularly those of an allergic disposition, the treatment will alleviate the severe symptoms but will not abolish them altogether. These patients require a maintenance injection of the highest dose they can tolerate at monthly intervals.

TREATMENT

Treatment depends largely upon the severity of the stinging and of the patient's reaction to it. The reaction is least with the honey bee and increases progressively with the humble bee, the wasp and the hornet.

When the sting is found it should be removed. It is a tiny black shaft with the white poison sac attached to its free end. It should never be removed by grasping its projecting end with forceps or fingers; this will express more venom from the poison sac. The sting should be scraped

from the flesh with the finger nail or the blade of a knife. If many stings have been received their removal can be tedious both for the patient and the operator; yet it must be carried out thoroughly and with care. Antiseptics should then be applied and sedatives may be necessary.

Occasionally the pain is so severe that local medication is necessary. Alkalis have little effect; this treatment, well known to the public, and still recommended in recent medical literature[9], is based upon the erroneous belief that the toxic factor of bee venom is formic acid. Gow[38] recommends vinegar and salt mixed in equal proportions rubbed well into the site of the sting. Strauss[101] has reported success with the antihistamine, phenindamine ('thephorin'), in the form of a 5 per cent. ointment. When gently massaged into the site of the sting, the pain was promptly relieved and local swelling was uncommon. Peake[86] has found tincture of iodine a useful remedy.

Stings in the mouth may cause considerable swelling of the mucous membrane of the air passages and tracheotomy may be required. The possibility of this emergency must be kept in mind and those stung in this region should have a prophylactic injection of adrenaline.

Adrenaline remains the best drug in the treatment of acute systemic symptoms. An intravenous dose of 5 to 15 minims (0.3 to 1 ml.) of 1: 1000 adrenaline should be injected slowly and repeated as is necessary. The use of antihistamine drugs is based upon the allergic interpretation of the generalized symptoms. Diphenhydramine ('benadryl') by mouth has been used with good effect[14] but at other times it has failed[83]. Absorption by this route is too slow to combat the rapid effects of the poison. A delay, of minutes, in the action of the drug can lead to a fatal outcome; effective drugs must be given parenterally. In any event it is better that antihistamines be used only in addition to adrenaline. When dangerous symptoms persist after stinging, despite the administration of adrenaline and antihistamine drugs, 25 mg. of corticotrophin in one litre of saline given during twenty-four hours by intravenous drip may be beneficial. Williams[112] used cortisone when a prolonged illness followed a wasp sting but acknowledged that corticotrophin, because of its more rapid action, would have been more valuable.

A few reports have mentioned the beneficial effects of calcium. Kelsey[57] believes that immunity can be acquired at the beginning of each season by taking 'ostocalcium', a preparation of calcium and vitamin D. He suggests a dosage of one tablet three times a day after food for the first two weeks, two tablets daily during the third week and one tablet daily during the fourth week. Thereafter, half a tablet is taken daily throughout the season. Intravenous calcium has been found effective in the control of severe reactions; it alleviates the generalized symptoms, in particular urticaria and œdema.

A patient, stung on the tip of the tongue, developed severe œdema of the tongue and face, together with a rash on the face and trunk. Dyspnœa and cyanosis developed

to such an extent that tracheotomy was considered necessary. An injection of calcium then produced immediate improvement and within half-an-hour only residual signs and symptoms remained[1].

Striking relief of symptoms also occurred in Koszalka's case[59] after the intravenous injection of calcium; adrenaline had previously proved ineffective. Two cases were also reported by Thews[103]. The beneficial effect of calcium in these cases is attributed to its alleged ability to decrease cellular and vascular permeability and to its antispasmodic action on smooth muscle. There is scanty experimental evidence of its value but Curphey and Solomon[21] investigated its efficacy in controlled experiments in the treatment of serum sickness and found it useful.

Calcium should be tried in all cases in which adrenaline has failed. A suitable dose would be 10 to 20 ml. of a 20 per cent. solution of calcium gluconate given intravenously, supplemented by 10 ml. of a 10 per cent. solution intramuscularly. The latter may be repeated in a few hours' time, if necessary.

PATHOLOGICAL AND POST-MORTEM FINDINGS

Bee venom has been shown to cause a localized necrosis, together with œdema and cellular infiltration at the site of a sting in unsensitized tissues[19, 110]. The reaction is maximal half-way down the sting at one hour; it then extends a little and becomes sharply defined in forty-eight hours. Kershaw, Crewe and Gordon[58] found that one hour after a wasp sting there was a scanty cellular infiltration, mostly by eosinophils, of the dermis. Twenty-four hours later there was a neutrophil polymorph infiltration; eosinophils were scanty. Considerable local œdema with muscular necrosis occurred in the area. Investigations on the action of wasp venom have shown necrosis of a sweat gland at the site of the sting.

Bee and wasp stings of the cornea[54, 102, 113, 114] have led to destruction of its substance and, when the venom is injected into the anterior chamber, injury to the anterior surface of the lens is likely to leave an opacity. The iris may be discoloured when the venom destroys the pigmented cells.

Necropsy following a fatal hypersensitive reaction to a bee or wasp sting usually reveals changes which, though characteristic, are slight and may be missed if the examination is perfunctory. There is no organic disease which will account for death. There is usually visceral congestion, and pulmonary œdema and some degree of œdema of the pharynx or larynx are present. In some cases pulmonary emphysema may be more notable than œdema and in yet others emphysema and œdema are of equal intensity. In my case pulmonary emphysema was combined with areas of dark red collapse. This is not mentioned by others but it has been noticed after sudden death from the therapeutic injection of foreign proteins[107]. Petechial hæmorrhages may be found in the skin or conjunctivæ or over the surface of the heart; larger areas of hæmorrhage may be seen beneath the endocardium of the left side of the septum.

When the sting of a bee or a wasp causes vasomotor collapse and death a diagnosis of allergic shock is confirmed by the foregoing changes. When a history of stinging is lacking it may be impossible to determine the cause

of death; the site of the sting may be obscure and the changes in the body are indefinite. In the latter event it is helpful if it be known that the deceased was hypersensitive to stings. It may be possible to obtain a positive Prausnitz-Küstner reaction. Lund and Hunt[66] demonstrated hypersensitivity to guinea-pig serum in a young woman who died a quarter-of-an-hour after an intracutaneous injection of 0.2 ml. of guinea-pig hæmoglobin. Several volunteers are required to receive the test sera as about 10 per cent. of persons do not react. Satisfactory wasp antigen is not yet available.

With the exception of drug idiosyncrasy, Lund and Hunt maintained that this reaction may demonstrate all forms of hypersensitivity likely to lead to sudden death. This is too optimistic a view. When positive, the results have value but negative results are often obtained with hypersensitive subjects. Thus, Benson[10] obtained a positive Prausnitz-Küstner reaction from only one of ten hypersensitive patients. Mueller and Hill[76] have suggested that passive transfer may be possible only in those persons with an inborn allergic disposition.

I wish to thank Professor C. J. Polson for his valuable help in the preparation of this article. I am indebted to Mr. Stephen E. Brown, H.M. Coroner for the Craven District of the West Riding of Yorkshire, for permission to publish the case record.

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This is a selection of the references which are likely to be of most interest to the general reader. The full list of references will be available with the author's reprints.

HYDRAMNIOS

By DAVID BYRON BROWN, M.B., M.R.C.O.G.
Registrar in Obstetrics and Gynæcology, The London Hospital

A survey has been made of the cases of hydramnios which were admitted to The London Hospital between the years 1948 and 1955, inclusive. Twenty-two cases, in which the loss of liquor was 60 ounces (1.7 litres) or more, or was obviously excessive at the time of rupture of the membranes, are reviewed. Most of these were clinically diagnosed from one to six weeks before delivery. Of the 12 patients delivered before the 37th week of pregnancy, as many as nine were suspected as having hydramnios for less than a week. As 7,230 mothers were confined during the eight years, the incidence of hydramnios was 0.3 per cent.

INCIDENCE OF ANOMALIES OF FŒTUS OR PLACENTA

The following anomalies were associated with 14 of the 22 cases of hydramnios, an incidence of 64 per cent.:—

7 with anencephaly (one was a binovular twin)—one acute hydramnios at 26 weeks.
1 with oxycephaly and syndactyly.
1 with meningomyelocele and spina bifida.
1 with achondroplasia and hydrocephalus.
1 with a sacrococcygeal tumour—acute hydramnios at 30 weeks.
1 with tracheo-œsophageal fistula.
1 with duodenal atresia.
1 with a placental chorioangioma—acute hydramnios at 28 weeks.

During the eight years of this survey, abnormalities were found in 104 new-born fœtuses and in one placenta. Hydatidiform moles are not included. Although there were 14 serious malformations associated with hydramnios, there were another 17 which were not. The fœtal loss was between 70 and 80 per cent. in each group. It would seem therefore that only a small percentage of malformed babies are accompanied by hydramnios. There is, however, a common association where there is a gross abnormality: one that is generally incompatible with life. It is interesting to note that two cases of anencephaly and eight of meningocele or meningomyelocele were not associated with hydramnios.

INCIDENCE OF TWIN PREGNANCIES

Of 133 patients delivered of twins, 37 sets were uniovular, there being 20 male and 17 female pairs. Only two sets of uniovular twins were complicated by hydramnios, and all four were male babies. In each case the hydramnios was acute in onset, one at the 28th week and the other at the 37th week of pregnancy. Although two of the babies did not survive because of immaturity, all four were apparently normally developed.

INCIDENCE OF HÆMOLYTIC DISEASE OF THE NEWBORN AND OF DIABETES MELLITUS

Hæmolytic disease of the newborn.—Two patients were included in this

series because in each case 70 ounces (2 litres) of liquor were surgically removed. Both fœtuses were stillborn. Other cases may have occurred in which the hydramnios has been obscured by the size of hydropic fœtuses.

Diabetes mellitus.—Of 30 diabetic mothers delivered, two had hydramnios. The babies were normally developed and both survived.

In two further cases there were no apparent reasons for the presence of hydramnios. One mother had advanced mitral stenosis, but the other was quite well. Seventy ounces of liquor (2 litres) were withdrawn from each patient.

COMPLICATIONS OF PREGNANCY AND LABOUR

The only serious *pregnancy* problem was respiratory distress caused by acute hydramnios. The complication occurred in the case associated with a placental chorioangioma, and it was relieved by abdominal paracentesis. No patients had pre-eclampsia but one had an accidental antepartum hæmorrhage when the membranes ruptured.

Labour complications.—Because of uterine inertia, two patients were delivered by Cæsarean section. In one of these cases, in which the fœtus was anencephalic, surgical and repeated medical inductions had all failed. There were no cases of prolapse of the cord, but postpartum hæmorrhage occurred three times.

FŒTAL MORTALITY

Twenty-two patients were delivered of 24 fœtuses; 15 were stillborn or did not survive beyond the neonatal period: a fœtal mortality of 68 per cent. Thirteen of the 15 losses were directly related to the associated disease or fœtal abnormality and not to the hydramnios. The other two were twins, their deaths from immaturity being due to acute hydramnios causing premature labour.

CASES WITH SLIGHTLY EXCESSIVE LIQUOR

In an additional twelve patients the amount of liquor at term was noticed either to be slightly excessive or was measured as between 30 and 50 ounces (0.85 and 1.5 litres). Two patients were delivered of abnormal babies: one mongol, and one binovular twin affected with a meningocele and hydrocephalus. The other 10 had uneventful pregnancies and their babies were all healthy.

CONCLUSIONS AND SUMMARY

(1) Hydramnios is uncommon, its incidence in this series of 7,230 patients being 0.3 per cent.

(2) There is a close association between hydramnios and gross fœtal malformations, particularly anencephaly.

(3) Hydramnios occurs as an occasional complication of diabetes mellitus, hæmolytic disease of the newborn and uniovular multiple pregnancies.

(4) Pre-eclampsia is not commonly associated with hydramnios. Uterine inertia and postpartum hæmorrhage are occasional complications.

I wish to thank Mr. Victor Lack, Mr. Alan Brews and Mr. Robert Percival for permission to review their cases, and also for their comments.

THE LEGAL ASPECT OF CERTIFICATION

By ALFRED H. HAYNES, F.W.I.
District Officer, Health Department, Kent

THE legal processes by which practitioners can secure the admission of mentally ill patients to appropriate hospitals are contained within the Lunacy Act, 1890, and the Mental Treatment Act, 1930. The latter enactment is supplemental and only makes provision for the admission to mental hospitals of those patients who, at the one end of the scale, are cooperative or who, at the other, are completely non-volitional. To secure inpatient treatment for that large group of in-between patients who refuse to act on medical advice, practitioners have no option but to invoke the provisions of the Lunacy Act, 1890. However much this may be deplored, the fact remains that the legislation of 1890 still remains the law.

A Royal Commission on the law relating to mental illness has been sifting evidence since early 1954, and its report is expected in the early future. Whatever recommendations the commissioners may feel disposed to make, however, it is quite certain that amending legislation, involving meticulous drafting, cannot be introduced for some time. Between the issue of the report of the 1924 Royal Commission and the coming into effect of the Mental Treatment Act, 1930, there was a lapse of four years. It seems quite clear therefore that there is no prospect of existing law and legal processes being dramatically swept away within the next few months.

It may well be asked why an Act of Parliament, introduced in an era when so little was known of mental illness and hedged about with such outmoded words as 'restraint', 'detention' and 'control', should have endured for so long. The answer lies in the preservation of both the principle relating to the freedom of the subject and the rule of law that none shall be confined but such as require confinement. For this reason, the power of the magistrate and interference with liberty are inseparable. Whether or not there is an over-emphasis on the judicial safeguards against illegal removal and detention, the fact remains that it is fundamental within British law, however medically necessary, that none except a judge or magistrate can deprive a person of his freedom. Were this not so, there is no question that the Mental Treatment Act, 1930, would have gone much further than it did.

Those who have read the verbal evidence and the written memoranda submitted to the Royal Commission will have learned that, whilst much has been said in criticism of the present law of certification, little has been said in its defence. The purpose of this article is neither to criticize nor to defend; the Lunacy Act, 1890, is law and, for better or for worse, its provisions must be adhered to. That being so, practitioners must continue to accept the fact

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that only those patients whose mental illness has sufficiently deteriorated to bring them within the scope of the Act can be removed to hospital against their will; there is no provision whatsoever in the Act for a period of observation.

THE ROLE OF THE MAGISTRATE

In the report of the 1924 Royal Commission (para. 30) it was stated that a person of unsound mind does not necessarily come within the purview of the Lunacy Acts. As to what constitutes unsoundness of mind, there is no legal definition; but, that it has something to do with a departure from normality, is beyond dispute. The Act places the responsibility of diagnosis on the practitioner—not, be it said, a diagnosis of a specific type of mental illness but a generalized certification that the practitioner has been led to a conclusion that the patient is 'a person of unsound mind *and* a proper person to be taken charge of and detained under care and treatment'. It is because of the additional final phrase that, so often, there is cleavage of opinion. Accepting the practitioner's conclusion that the patient is a person of unsound mind, the magistrate will not always accept the conclusion that he is necessarily a proper person 'to be taken charge of and detained'. The truth is that insanity of such a degree that it necessitates the patient's forcible removal from the community is not always a definitely ascertainable state—it is a matter of degree upon which there must often be room for honest difference of opinion. If magistrates are not to become mere rubber-stamps and so bring the whole of the existing code into disrepute, the factor of this independent judgment must be recognized. In my experience, magistrates refuse to make a reception order in approximately 10 per cent. of the cases referred to them.

WHEN TO CERTIFY

At what stage in mental illness is a practitioner justified in invoking the law of certification? The clues to the answer to this all-important question bear no definite shape. Even when the procedures laid down in the 1890 Act are examined, all that is revealed is the hazy outline of fog-beshrouded principles. Primarily, the responsibility for setting the legal machinery in motion rests upon the lay local health authority officer known as the duly authorized officer but it should be noted that he has no statutory authority whatsoever to invoke the law until he has established reasonable grounds for believing that the patient is both a person of unsound mind *and* a proper person to be sent to a mental hospital. To belief on these two points the officer must add personal satisfaction—satisfaction that the patient is either not under proper care and control or that relatives are unable or unwilling to proceed by way of private petition. Not until all these prerequisite conditions are satisfied is there placed on the duly authorized officer a legal obligation to notify the case to a magistrate.

What emerges from the foregoing is that the present law is not so much concerned with medical desirabilities as it is with ensuring that only those who are '*proper*' persons requiring '*proper*' care and control are sent to

mental hospitals under judicial orders. Although the italicized word is capable of having many constructions put upon it, the view of the 1924 Royal Commission was that restriction of liberty can only be justified when 'the instability has reached the stage of being a danger to the sufferer himself or to his neighbours or is such that the patient is incapable of managing himself'. In other words, there is no justification in law for certification unless and until a mentally ill patient's behaviour, attitude or speech exhibits trends that contravene the accepted standards of personal and social conduct. In cases of real urgency when either the public safety or the patient's welfare is endangered, the duly authorized officer may choose between using his three-day order powers (unfortunately only valid for certain designated hospitals), cooperating with the practitioner in the completion of an urgency order or notifying a magistrate.

THE METHOD OF CERTIFICATION

Assuming that the patient is one in respect of whom the duly authorized officer has a duty to perform, the sequence of events is as follows:—

(a) Within three days, the duly authorized officer must give notice to a magistrate having jurisdiction in the place where the patient is.
(b) On receiving the notice, the magistrate must direct the duly authorized officer to bring the patient before him or some other magistrate. This may be at the patient's own home. The maximum period allowed between the receipt of the officer's notice and the bringing of the patient before the magistrate is three days.
(c) The magistrate must call in a medical practitioner whose duty it then becomes to advise the magistrate as to whether or not the patient is considered to be of unsound mind.
(d) The magistrate must himself examine the patient and make such other inquiries as he thinks advisable.
(e) If the magistrate is satisfied that the patient is a proper person to be detained in a mental hospital, then (provided that the practitioner has completed a certificate in the prescribed form) he may summarily order that the patient shall be detained in a named hospital. The operative word in the Act is 'may' and, even although the practitioner has completed a certificate, it is entirely within the prerogative of the magistrate as to whether or not he shall make an order. It is also within the magistrate's discretion as to whether or not, in lieu of ordering the patient's detention, he should allow a relative or friend to retain or take the patient under his own care; the only proviso to this is that the magistrate must be satisfied that the relative or friend is able to take proper care of the patient.
(f) If the magistrate makes a summary reception order, it is then the duty of the duly authorized officer to convey the patient to the hospital named in the order forthwith.

Such then is the strict sequence of events which the law demands in relation to the certification and removal of mentally ill patients from their own homes; in cases in which the patient is wandering at large, there is a slight modification in procedure. In actual practice, of course, the magistrate, practitioner and duly authorized officer usually meet by appointment at the patient's house. It is important to note, however, that not only does the magistrate's judicial order make the specific statement that he has called to his assistance a registered medical practitioner but that the Act precludes the signing of the medical certificate by any practitioner other than the one whom the magistrate has called in. In partnership practices especially, this

legal nicety is one of importance. Moreover, the choice of practitioner is entirely within the magistrate's discretion.

Although the term 'certification' is generally used to refer compendiously to the whole procedure, in actual fact it is the practitioner who does the certifying. The medical certificate is hedged about with a number of safeguards. The more important of these are:—

(a) Every medical certificate under the Act must be made and signed by a doctor. The statutory form of the certificate restricts the power of issue to practitioners, being registered under the Medical Act, 1858, who are in actual practice of the profession.
(b) Every medical certificate must be factual: i.e. it must state the facts upon which the certifying practitioner has formed his opinion that the patient is of unsound mind. It is incumbent on the practitioner to distinguish between the facts observed by himself and the facts communicated to him by others.
(c) Personal examination by the certifying practitioner is essential. A magistrate cannot make a reception order upon a medical certificate which is founded only on facts communicated by others.
(d) Every medical certificate is evidence both of the facts stated therein and of the judgment formed by the certifying practitioner. It has the same legal value and effect as if the matters appearing therein had been verified on oath.
(e) The practitioner's examination of the patient must take place within seven clear days of the date of the making of the reception order.
(f) If, in the opinion of the certifying practitioner, the patient is not in a fit state to be removed, then a certificate to this effect must be completed. Its effect is to suspend the patient's removal to hospital until the certifying practitioner, or some other practitioner, certifies the patient fit to be removed.
(g) If, to prevent the patient from injuring himself or others, mechanical means of bodily restraint are applied, then a supporting medical certificate describing the mechanical means employed and the grounds for their use shall be given. In cases in which drugs are employed to sedate or quieten the patient during the removal, then the reception order should be endorsed accordingly.
(h) A practitioner may not sign a medical certificate if:—
    (i) he is the manager of the institution into which the patient is to be received;
    (ii) he is a person who is interested in the payments on account of the patient;
    (iii) he is a regular medical attendant of the institution in which the patient is to be detained;
    (iv) he is related to the patient either by blood or by marriage or is the partner or assistant of such a relative.

THE BOARD OF CONTROL

Every medical certificate incorporated in a reception order (as, indeed, is the whole order) is subjected to the most careful scrutiny by the Board of Control and it is not unusual to find, after a patient's admission, that the order is returned to the certifying practitioner for amplification of facts or amendments. The duty exercisable by the Board of Control in this respect is to ensure the legality of the patient's detention and, no matter how slightly imperfect the instrument, the Board has no hesitation in returning incorrect or defective certificates. The practitioner's amendment must be made within a period of fourteen days after the date of the patient's reception in the hospital. That meticulous care is necessary in the recording of facts on the medical certificate is evidenced in section 34 of the 1890 Act which empowers the Commissioners of the Board of Control to order the patient's discharge in any case in which they deem the certificate to be incorrect or defective.

PROCEEDINGS FOR ILLEGAL REMOVAL

From what has been said, it will clearly be evident that, far from being a universal resolver of social problems, outmoded and outdated though it be, the Lunacy Act, 1890, is very clear on the issue that none shall be certified except such as are legally certifiable. On this subject, the 1924 Royal Commission (as will probably the 1954 Royal Commission) had much to say. What is not generally realized is that not only does certification take away from a patient his democratic right to regulate his life in his own way but it also denies him the right, while detained, to enter into even the simplest of contracts or manage his own affairs. It needs to be borne in mind that, whilst a person who signs a medical certificate is not liable to any civil or criminal proceedings if he acts in good faith and with reasonable care, a patient who considers that his forcible removal to, and detention in, a mental hospital has been illegally procured has a right of action in the courts. Embodied within every medical certificate is a declaration that the practitioner is aware of section 317 of the Lunacy Act; this reads that any person who makes a wilful misstatement of any material fact in any medical or other certificate, or in any statement or report of bodily health or mental condition under the Act, shall be guilty of a misdemeanour.

The right of a patient to institute proceedings for illegal removal and detention accrues on discharge from hospital. In view of the provisions which now give power to a relative to direct the discharge of a patient (irrespective of the degree of mental illness or whether or not the patient is recovered), the right of action—which, if successful, involves the payment of substantial damages—is one not to be dismissed lightly. A patient desiring to institute proceedings must do so within twelve months from the date of his release from the hospital. In view of the importance of affording protection to those whose duty it is to apply the provisions of the Act, certain amendments to the 1890 legislation were made by the Mental Treatment Act, 1930. The following extract gives indication of the measure of protection now afforded:—

> Where a person has . . . signed . . . or done any act with a view to signing . . . a recommendation or certificate . . . he shall not be liable to any civil or criminal proceedings whether on the ground of want of jurisdiction or on any other ground unless he has acted in bad faith or without reasonable care.
>
> No proceedings, civil or criminal, shall be brought against any person in any court in respect of any such matter as is mentioned in the last preceding subsection without the leave of the High Court, and leave shall not be given unless the court is satisfied that there is substantial ground for the contention that the person against whom it is sought to bring the proceedings has acted in bad faith or without reasonable care.
>
> Notice of any application under the last preceding subsection shall be given to the person against whom it is sought to bring the proceedings and that person shall be entitled to be heard against the application.
>
> Where, on any application under this section, leave is given to bring any proceedings, and the proceedings are commenced within four weeks after the date on which leave was so given, the proceedings shall, for the purposes of the Public Authorities Protection Act, 1893, be deemed to have been commenced on the date on which notice of the application was given to the person against whom the proceedings are to be brought.

GENERAL PRACTITIONERS' FORUM

THE TOOLS FOR THE JOB

MIDWIFERY IN GENERAL PRACTICE

By R. P. C. HANDFIELD-JONES, B.M., M.R.C.P., D.Obst.R.C.O.G.
Haddenham, Buckinghamshire

Attending a woman in childbirth in her own home can be one of the greatest joys that general practice has to offer, an antidote to too much paper work and minor illness. Two conditions must be fulfilled: all cases booked for home confinement must be normal so far as careful antenatal care can ensure, and the doctor must be well equipped.

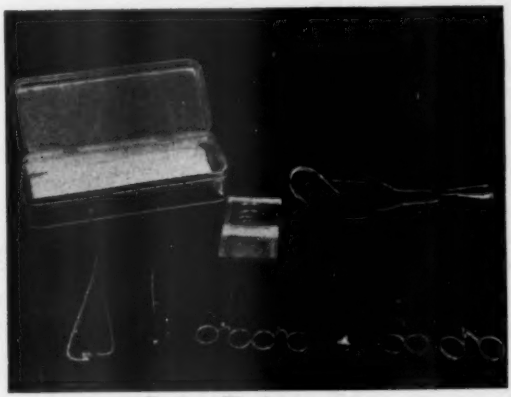

Fig. 1.—The instruments.

I remember doing a locum tenency for a senior and respected doctor. I took his midwifery bag to the first confinement and found inside an empty chloroform bottle, a pair of rusty artery forceps, several yards of silkworm gut and one blade of a pair of obstetrical forceps. The other blade I found some time later in the garage, where it had been used to open a crate of 'Scotch'. The story has a happy ending: the baby was safely delivered by the district midwife.

In general practice we have the job of providing and looking after our equipment; cleaning and sterilizing instruments and gloves is another of the many chores that fall to the general practitioner. In hospital it was easy. Sister waited on us with tastefully prepared trolleys of sterile instruments and the junior probationer cleared up the mess afterwards. Our problem is to provide the tools for the job in a form that is easily kept in order and carried about.

The following notes illustrate one way of doing it; I hope they will provoke readers to describe others.

THE EQUIPMENT

I carry six articles in the car: a midwifery bag, a dressings drum, a lamp, a

'trilene' inhaler, a lithotomy frame and a box of transfusion equipment. Since the district midwife and I attend all confinements together, I do not carry the dressings, bowls and basins which she provides.

THE BAG

This is a simple chest-of-drawers type of case with three drawers. In it are packed the necessary instruments, drugs and antiseptics.

FIG. 2.—The dressings drum.

The instruments are the following (fig. 1):—

Wrigley's forceps
Needleholders
Scissors
Sponge forceps
Mosquito forceps
Toothed dissecting forceps
Vulval retractors
Needles: Mayo, trochar pointed, half circle, size 2; curved, triangular pointed, size 7
Nylon sutures
Catgut: strength 00.

The instruments are packed in a tin and sterilized by dry heat in a hot-air oven sterilizer. After the tin has cooled it is taped round with adhesive tape to keep it airtight; the instruments remain sterile and are ready for immediate use. There is no need to carry round a portable sterilizer and time is not wasted at confinements in boiling up the instruments. The nylon sutures will stand sterilizing at 160°C. once, but become brittle if reheated. The tubes of catgut are kept in corked test-tubes containing 1 in 1000 mercury biniodide.

One 2-ml. all-glass syringe and one 20-ml. all-glass syringe are sterilized within heavy glass test-tubes. With the large syringe there is a 5-inch (12.5 cm.) 24 B.W.G. needle for pudendal block.

These instruments are adequate for a low-forceps delivery and repair of the perineum under pudendal block anæsthesia. I do not believe that anything more involved should be undertaken in the home. I do not put on forceps unless I can see the vertex, so I have no need to carry axis-traction forceps. There is a hospital six miles away and it is far better for the patient to be transported there during the second stage should obstetrical intervention be necessary than to get into difficulties in the home and possibly be landed with the disaster of a failed forceps delivery.

Drugs and antiseptics include:—

Amylobarbitone sodium ('sodium amytal'), 3-grain (0.2 g.) capsules
Diamorphine hydrochloride, 1/12 grain (5 mg.)
Lignocaine hydrochloride, 0.5 per cent. solution
Ergometrine maleate, 0.5 mg.
Nalorphine ('lethidrone'), 10 mg.
Chlorhexidine ('hibitane'), 0.05 per cent. solution in 0.5 per cent. cetrimide ('cetavlon')
'Hibitane cream'.

Also carried in the bag are rubber gloves, rubber apron, masks and fœtal stethoscope.

THE DRESSINGS DRUM

Gauze swabs, cotton-wool balls and two linen towels are packed in a nine-inch (23 cm.) drum (fig. 2), with two stainless-steel gallipots and a rubber catheter and mucus aspirator. The drum is autoclaved at the local hospital. The rubber catheter and aspirator will stand several exposures to full steam pressure but need to be replaced at the first sign of perishing.

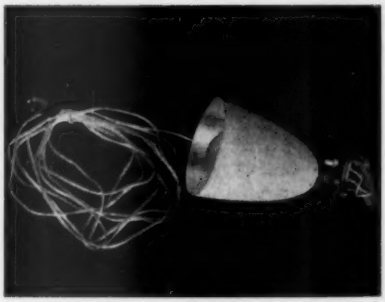

FIG. 3.—The lamp.

THE LAMP

Good lighting is essential for careful repair of the perineum and the most convenient lamp has a spring clip which will attach to the back of a chair. A 60-watt bulb in a metal reflector gives all the light needed and a long lead with a two-way adapter is important (fig. 3). If the patient lives in a cottage without electricity I do not undertake to look after her at home, but insist on hospital booking.

THE LITHOTOMY FRAME

To my mind the biggest problem lies in keeping the patient in the right position. Of course, for a normal delivery the left lateral is the easiest and it is the safest when a general anæsthetic is used. With pudendal block, low-forceps delivery and repair of the perineum are best done with the patient in the lithotomy position and the frame (fig. 4, 5) is designed to hold the

legs in this position and to fit into any sort of bed. It consists of a horizontal portion which slides under the mattress and vertical posts which attach to the horizontal part. The patient lies across the bed with her buttocks at one edge; her weight keeps the whole thing steady and her feet are supported in stirrups on the vertical posts. The frame prevents the woman sinking into a sagging mattress and her attendants are spared the backache.

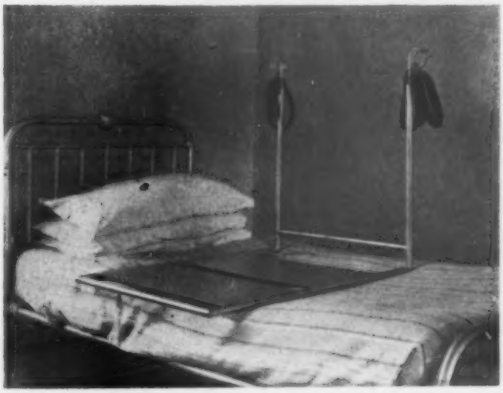

FIG. 4.—The lithotomy frame.

The frame is made of tubular steel and aluminium sheet; the vertical and horizontal parts come apart for travelling and will fit into any small car.

PROCEDURE

When the equipment has been assembled in the patient's house it remains to lay it out so that everything is to hand and to ensure that the instruments and dressings remain sterile until used.

First the 'dirty' jobs are done. The lithotomy frame is slid under the mattress, and the lamp is connected up and fixed to a chair. A table or chest of drawers is selected to serve as an instrument table. The bag is unpacked and the bottles of antiseptic and local anæsthetic are placed on the table. The tin of instruments and the drum are opened but the contents are not touched.

FIG. 5.—The lithotomy frame in position.

Next the hands are washed and dried, the gloves, which are not sterile, are washed on the hands and treated with 'hibitane cream'. One of the sterile towels from the drum is then laid on the table and the sterile instruments and dressings laid out thereon.

The district midwife completes the preparations by unwrapping the 20-ml. syringe and tipping it out of its tube on to the sterile towel. She pours the chlorhexidine-cetrimide mixture into a gallipot, puts the patient's legs into the stirrups of the lithotomy frame and everything is ready.

I am indebted to Mr. R. G. Mason, F.I.B.P., of Stoke Mandeville Hospital, for the photographs. The lithotomy frame is made by Thame Engineering (Oxon) Ltd., Haddenham, Bucks., who have applied for a patent.

THE TREATMENT OF SUNBURN

By D. A. HASTINGS, M.R.C.S., L.R.C.P.
Torquay, Devon

It appears perhaps rather trivial to write at such length about the treatment of sunburn in this country but, looking through the medical journals, it certainly does not seem to be a subject which has been considered at much length.

CLASSIFICATION AND INCIDENCE

These cases of sunburn can represent quite a fair amount of the work in hospitals in busy seaside resorts during the summer. During the summer of 1955 I was a house officer at the Torbay Hospital, Torquay, and during the three-month period, July to September, we dealt with 171 cases of sunburn in the casualty department. These were classified as follows:—

Type of burn	No.	%
1st degree burn	76	44.4
2nd degree burn	56	32.7
Œdema of eyes and face only	30	17.5
Heat stroke	5	2.9
Herpes labialis (facial)	3	1.8

TABLE I.—Classification of 170 cases of sunburn.

1st degree burns: erythema.

2nd degree burns: erythema plus blister formation.

3rd degree burns: involving skin, subcutaneous tissue and muscle.

In addition to these groups, an increasing number of people presented themselves with one or more of the following features:—

Œdema of the eyes and face.

Œdema of the arms.

Œdema of the legs and ankles, simulating the well-known 'deck ankle' experienced on troopships.

Table I shows the number of cases which fell into each of these groups.

TREATMENT

As the majority of the patients concerned were holidaymakers, it was obvious that the treatment had to be efficient and quickly effective so that they were not taken away from their normal enjoyment in the short time they were on holiday. The following scheme of treatment was therefore instituted, and appeared to work very satisfactorily.

1st degree burns.—Advice was given to remain out of the sun for forty-eight hours, and to apply the following paste, spread on lint or gauze, to the affected area:—

Boric acid	0.5 per cent.
Eucalyptus	0.5 per cent.

If pain was severe, a sedative was prescribed, usually quinalbarbitone sodium, 1½ to 3 grains (0.1 to 0.2 g.) at night.

2nd degree burns.—Treatment was given as above, except that, in addition, the blisters were incised aseptically and, after twenty-four to forty-eight hours, penicillin powder and open-air treatment were prescribed. Complete sheltering from the sun was advised, and again sedatives were used at night. With the severe 2nd degree burns, with evidence of mild heat stroke, salt water was given immediately and advised for three days.

Œdema of eyes and face.—This was usually found in people who had been gazing into the sun for a fair length of time, wearing sunglasses, and accordingly the patient was told to keep out of the sun, not to wear glasses and, in the case of women, to wear a large sun hat. In addition, diphenhydramine ('benadryl') or mepyramine ('anthisan'), in a dosage of 50 to 100 mg. three times a day, was given.

If the patient was staying for any length of time, a course of promethazine ('phenergan'), 25 mg. twice daily for about four days, was advised, following the emergency treatment with diphenhydramine. In addition, the patients were asked to reduce the amount of water taken to about three pints (1.75 litres) a day, according to the severity of the heat. This was usually only necessary for about forty-eight hours.

Œdema of hands, legs and feet.—Similar treatment to the above was given, except that elevation of the affected part was advised until the swelling had subsided.

This emergency treatment of sunburn was rounded off by giving strict advice, to adolescents and adults alike, on the dangers of sunburn. All in all it appeared to work very well.

The summer of 1956 produced nothing like the same crop of cases of sunburn, but the same line of treatment was followed with equally satisfactory results.

I am indebted to the staff of the casualty department at the Torbay Hospital for their cooperation.

LAENNEC

By ROBERT THOMPSON, M.B., B.Ch., D.P.M.
Formerly Consultant Psychiatrist, St. Crispin Hospital, Duston

While on a holiday in Brittany, in the summer of 1955, I had a delightful experience. During my stay in Quimper, I came across, quite by accident, the statue erected to the memory of Laennec, which is in the square surrounding the famous cathedral.

HIS STATUE

The statue, which is in bronze, is about life-size, and it shows Laennec seated on a pedestal about eight feet high (fig. 1). Laennec is shown in

Fig. 1.—The statue of Laennec which stands in the cathedral square at Quimper.

academic robes, with legs crossed. The right hand, holding a scroll, rests against his left knee, while the left hand is raised, with the forefinger pointing, as if he were emphasizing a point to a class of students. The features are small and finely moulded, with that refinement of feature which is so characteristic of the Bretons in that area, and the expression is thoughtful. There is an abundant crop of wavy hair, which is not surprising,

as Laennec died at the early age of 45. The single word LAENNEC is on the front of the pedestal, and on the back of the pedestal there is the following inscription.

A L'INVENTEUR DE L'AUSCULTATION.
LAENNEC, RENÉ THÉOPHILE HYACINTHE.
NÉ À QUIMPER LE 17 FÉVRIER, 1781.
MORT À PLOARÉ EN 1826.
PROFESSEUR À LA FACULTÉ DE MÉDECINE DE PARIS,
ET AU COLLÈGE DE FRANCE.
MEMBRE DE L'ACADÉMIE DE MÉDECINE.
CE MONUMENT A ÉTÉ ÉLEVÉ PAR L'ASSOCIATION
GÉNÉRALE DES MÉDECINS DE FRANCE.
PAR LA BRETAGNE.
ET PAR LES MÉDECINS FRANÇAIS ET ÉTRANGERS.
MAI 1868.

Underneath the chair on which Laennec is seated are several large sculptured 'volumes'. These are flanked on the left side by a laurel wreath, and on the right side by an open scroll on which is written the single word, AUSCULTATION. On the left side of the pedestal, on the stone underneath the chair, is inscribed what is presumably the sculptor's name, 'E. Le Quesne 1867'.

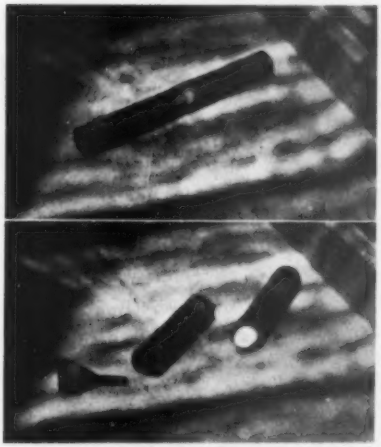

FIG. 2.—Laennec's stethoscope which is in the museum at Quimper.

HIS STETHOSCOPE

Again, almost by accident, I heard that Laennec's stethoscope was in the local museum (Musée des Beaux-Arts) a few yards away, and the curator very kindly allowed me to measure and photograph this historic instrument (fig. 2, 3).

The stethoscope is a round, solid, compact, beautifully tooled instrument, in lightish brown, polished hardwood. It can be 'disarticulated' into three pieces (presumably for convenience in carrying): two sections of equal length and an 'end piece'. The total length of the 'articulated' instrument is 12.7 inches (32.25 cm.). The 'end piece' is a brass tube 3 inches (7.5 cm.) long, inserted into a wooden cone, with 1.4 inches (3.5 cm.) of brass tube projecting. Cone and tube fit most beautifully into one end, and when 'articulated' the wooden portion of the cone, which flushes with the rest of the instrument, measures 6 inches (15 mm.). One of the sections is 'articulated' with the other by means of a hollow projecting ivory screw, the length of which is 6 inches (15 mm.) and the circumference 2.7 inches (6.9 cm.).

The first thing that I think would surprise the present-day doctor is the

'stoutness' of the instrument (it is 1.6 inches [4 cm.] in diameter). The next surprising thing is the smallness of the aperture relative to the diameter (only .4 inch [10 mm.]). The third surprising thing (perhaps not so surprising in that land of lovely precision), is the beautiful finish, down to the ivory screw which unites the two equal sections.

I used the instrument (by the very kind graces of the curator) to listen to my daughter's heart, and to the sounds of a wristlet watch, and the sounds I thought came through with great purity, though much more audibly (quite loud in fact) when the 'end piece' was removed and a correspondingly greater area of chest wall taken in. In using the instrument one understands

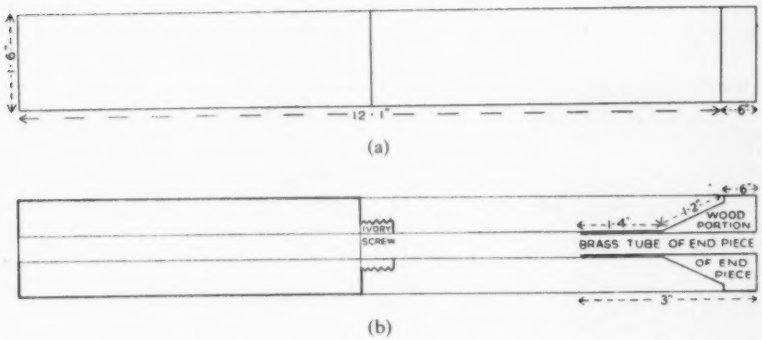

FIG. 3.—Laennec's stethoscope. (a) Profile view; (b) Cross section.

the reason for its 'stoutness', as the ear lies most comfortably on its broad diameter. The faded inscription on the little card in the museum simply bore the words: 'Cylindre (Stethoscope) de Laennec'.

THE SORBONNE MURAL

Later, when in Paris, again quite by accident, I came across a large mural in the Sorbonne depicting Laennec with a class of students. The inscription underneath read: 'Laennec à l'hôpital Necker Ausculte un Phtisique devant ses élèves 1816'. The mural shows Laennec seated on the left-hand side of a bed, facing the foot of the bed. In the bed there is sitting up an emaciated middle-aged man, and Laennec's right hand is placed on the man's back, in the region of the base of the lungs. In his left hand, which rests on the coverlet, there is this identical stethoscope, fully articulated. Laennec's head is turned sharply to the left, towards four or five rather mature-looking students who are respectfully grouped behind a Sister (dressed in nun's habit), and he would appear to be outlining a history of the case before proceeding to the actual examination.

CURRENT THERAPEUTICS

CXIV.—OLEANDOMYCIN

By ROBERT CRUICKSHANK, M.D., F.R.C.P.

Principal, Wright-Fleming Institute for Microbiology, and Professor of Bacteriology, St. Mary's Hospital Medical School

THE present-day approach to the rational use of antimicrobial drugs by the practising doctor will largely depend upon whether most of his patients are in hospital or at home.

INTRODUCTION

In the hospital environment, where infections will tend to be more severe, laboratory facilities are readily available so that the first requirement for rational chemotherapy—to treat specific infections and not clinical syndromes—is more easily met than in general practice. Again, it is safe to assume that the patient is having his drugs in the doses and at the times prescribed while injections of drugs that have to be given parenterally are more easily arranged. On the other hand, in the hospital environment there is likely to be a much higher incidence of infecting pathogens that are drug-resistant since these drug-resistant bacteria are spread around the wards in various ways and patients become secondarily infected with them. For example, the incidence of penicillin-resistant staphylococci in hospitals may range around 60 to 80 per cent., whereas in general practice it is more likely to be around 15 to 25 per cent. Indeed, it is the common experience that whenever a new drug is used freely among hospital patients, the incidence of pathogenic bacteria resistant to that particular drug steadily increases. This has proved to be the case with streptomycin, the tetracyclines and erythromycin, but to a less extent with chloramphenicol.

Routine testing for drug sensitivity of bacterial pathogens isolated from patients in hospital is therefore all the more important while the hospital doctor is correspondingly more interested in the availability and activities of new drugs. For similar reasons many hospital authorities have restricted the use of erythromycin, which acts rather like penicillin, because it was until recently the most suitable, and at times the only, alternative to penicillin for the treatment of patients with penicillin-resistant staphylococci. But there seemed no good reason for a similar restriction of this drug in general practice since resistance to it develops rather slowly, whilst it has an advantage over penicillin in being readily absorbed from the gut and over the tetracyclines in the reduced risk of side-effects and complications. However, the broad-spectrum antibiotics, such as the tetracyclines and chloramphenicol, have an appeal for the general practitioner for whom laboratory facilities may be less easily available, although doctors often do

not make contact with the hospital laboratory which is ready and willing to help them.

These broad-spectrum antibiotics may be expected to be active against a fairly wide range of bacterial infections but they have certain disadvantages. (1) They are bacteriostatic, not bactericidal, so that clinical improvement, is often not accompanied by bacteriological cure; for example, in streptococcal sore throat, the tetracyclines are intermediate between the sulphonamides (ineffective) and penicillin (highly effective) in eliminating the hæmolytic streptococci, and this may be important in relation to the prevention of both septic complications (e.g. adenitis, otitis media, sinusitis) and non-septic complications (rheumatic fever, glomerulonephritis). (2) They produce nausea and intestinal upset in a variable proportion of patients and this may lead to refusal by the patient to continue with treatment for the less severe infections. (3) They may predispose to secondary infection by dangerous organisms that replace the eliminated normal harmless bacteria in the mouth and gut, e.g. monilial infections and the less common, but sometimes, fatal staphylococcal enterocolitis. (4) They are bitter drugs and are usually prescribed in capsules which young children and some older patients cannot swallow.

THE PRESENT POSITION

It is against this background that in the past few years a series of new antibiotics has been introduced which have a more restricted antimicrobial activity. Like penicillin, they are most effective against the gram-positive bacteria and are therefore less likely to lead to secondary infections with 'replacement flora'; they have the additional advantage that they are more bactericidal than bacteriostatic. The first of these drugs was erythromycin, the properties and clinical applications of which were described in *The Practitioner* last year (Maclean, 1956). Then came, in turn, spiramycin which was reviewed in 'Current Therapeutics' early this year (Lepper, 1957), and which closely simulates erythromycin except that on a weight basis the latter drug is 4 to 20 times more active; novobiocin discovered independently by three different laboratories and therefore also known as 'albamycin' (Upjohn Company, and not to be confused with the Russian drug 'albomycin'), 'cathomycin' (Merck) and 'cardelmycin' (Pfizer); this drug is active against various gram-positive organisms and particularly staphylococci which, however, easily develop resistance to it; vancomycin ('vancocin', Eli Lilly) which is less active than erythromycin or novobiocin against staphylococci and has the disadvantage of having to be given intravenously because it is not absorbed from the bowel and causes pain on intramuscular injection; and oleandomycin ('matromycin', Pfizer; 'romicil' Roche) which is to be discussed more fully in this article.

ANTIMICROBIAL SPECTRUM AND PHARMACOLOGY OF OLEANDOMYCIN

The attractively named oleandomycin, derived from a strain of *Streptomyces*

antibioticus, is prepared as the mono-hydrochloride salt (it is also available as the phosphate), a white crystalline compound which is soluble in water up to 5 per cent. It is active against such gram-positive organisms as staphylococci, streptococci, pneumococci, the anthrax bacillus, erysipelothrix and the anaerobic clostridia, and against the gram-negative diplococci (gonococcus and meningococcus), *Hæmophilus pertussis* and *H. influenzæ* and, less actively, against the brucella, mycobacteria, rickettsiæ and the larger viruses. It is ineffective against the gram-negative bacilli exemplified by the coliform group, the salmonellæ and shigellæ, proteus and pyocyanea (Sobin *et al.*, 1954-55).

It is difficult to draw a clear dividing line between bacteriostatic and bactericidal activity; the former is usually measured by the minimum concentration of the drug required to inhibit the growth of the test organism in broth or in solid medium, whereas bactericidal activity is determined by the killing effect (as demonstrated by serial bacterial counts) of a certain concentration of the drug on a young culture of the organism growing in a liquid nutrient medium. No such comparisons seem to have been made in the case of oleandomycin.

Resistance of *Staphylococcus pyogenes* to oleandomycin seems to develop in a slow, adaptive (or many-step) fashion (Noyes *et al.*, 1956) rather as in the case of erythromycin, and in contrast to the rapid development of resistance to novobiocin (Jawetz *et al.*, 1957). In cross-resistance studies, two different patterns seem to have emerged. Staphylococci that have been rendered resistant to oleandomycin also develop resistance to erythromycin and vice versa, whereas there is no cross-resistance with novobiocin. Following a report by Ross (1956), however, of the isolation from patients of erythromycin-resistant strains of *Staph. pyogenes* that were sensitive or only moderately resistant to oleandomycin, Needham and Geraci (1956) found that 54 out of 75 (72 per cent.) of erythromycin-resistant strains of *Staph. pyogenes* from clinical sources were sensitive to oleandomycin; this apparent difference between clinically resistant and *in vitro* resistant strains needs further study. There is no cross-resistance with penicillin, streptomycin, the tetracyclines or chloramphenicol.

Absorption from the gut after oral administration of the drug in capsules containing 0.5 to 1.0 gramme doses seems to be satisfactory; the drug is demonstrable in the blood within one hour and with the 1.0 gramme dose is well maintained for eight to twelve hours. Blood levels of 7 to 10 mcg./ml. are quoted, although in the study by Baadj *et al.* (1957), much lower levels (in the range of 0.5 to 2.5 mcg./ml.) were reported. The drug is excreted in concentrations up to 2000 mcg./ml. in the urine but does not easily pass into the cerebrospinal fluid. High concentrations are said to occur in the bile.

CLINICAL USES

There have been no clinical reports so far of the use of oleandomycin in this country and only a limited number of clinical studies have appeared in

the American and continental literature. With the easy availability of a wide range of antimicrobial drugs and the public expectations of their administration in suitable (and unsuitable) cases, it has become very difficult to organize controlled clinical trials of any new antibiotic that has an action similar to previously existing drugs. It seems a pity, however, that trials of the kind that were carried out when the tetracyclines and chloramphenicol first became available are not being arranged for these new drugs. For example, the clinical comparison of chlortetracycline and chloramphenicol against the standard chemotherapy (penicillin or sulphonamides) in the treatment of adult pneumonia, which was carried out in four co-operating hospitals, showed that these new drugs had no obvious advantages over the established drugs and had the disadvantages of being more expensive and causing gastro-intestinal upset in a proportion of cases (Report, 1951). A similar comparison of, say, erythromycin and oleandomycin on the one side, against penicillin or sulphonamides, in the treatment of the pneumonias of children or adults would be informative. Meanwhile we can but report and comment on the uncontrolled clinical studies. Most of these concern acute infections of the respiratory tract and staphylococcal infections.

The drug is available in capsules of 100 mg. and 250 mg.

PNEUMONIA

Ross (1956) treated 20 cases of pneumonia in children, aged 15 months to 10 years, in doses of 40 mg./kg. body weight, given daily in a six-hourly divided dosage for periods of five to seven days. Throat cultures, blood cultures, blood counts and x-ray examinations were done on admission and at intervals during treatment. Admission temperatures ranged from 100.4° to 104.2° F. (38° to 40.1° C.), and white cell counts exceeded 12,000 per c.mm. in 18 of the 20 cases, which were classified as regards their illness as mild (8), moderate (7) and severe (5). All cases were regarded as bacterial pneumonias although a specific pathogen was recovered from only seven cases (pneumococci in six, *H. influenzæ* type B in one). The results, based principally on the rapidity of return to normal of clinical, radiological and laboratory findings, were good in 14 cases and fair in six, temperatures falling to normal within 24 to 48 hours in 14 cases and within three days in the remaining six. The clinical response in this small group of pneumonias in children was regarded as similar to that ordinarily obtained with penicillin or erythromycin. There were practically no ill-effects. Essellier and Keith (1956) reported good results in 48 out of 52 cases of presumed bacterial pneumonia (patients afebrile and clinically markedly improved within two to three days) on doses of 1.5 to 3 g. daily. The four patients who did not respond were cases of aspiration pneumonia with a varied bacterial flora (*E. coli*, proteus and various streptococci). Bernstein and Pillar (1956) also reported favourable responses in a small series of nine cases, particularly in the five cases of specific bacterial etiology. Hegglin

et al. (1956) treated 56 patients with primary, and 31 with secondary, pneumonia; the over-all results were considered to be satisfactory although in the few cases of Q fever, tetracycline was more effective. These authors also claimed good results in 25 cases of bronchitis and bronchiectasis.

STAPHYLOCOCCAL INFECTIONS

Hegglin *et al.* (1956) used oleandomycin systemically in 31 cases of skin infections, mostly staphylococcal including some penicillin-resistant strains, and obtained good responses in 21 and delayed improvement in six cases. Other authors have also claimed satisfactory results in staphylococcal furunculosis, osteomyelitis and urinary-tract infections, whilst Ross (1956) reported substantial improvement within one to four days in a series of 13 children with acute diarrhœa from whose stools a profuse growth of *Staph. aureus* was obtained. These were not cases of post-chemotherapy enterocolitis and it is not certain whether the staphylococci were the causative agents or merely an adventitious finding.

THROAT INFECTIONS

Several authors have reported favourably on the treatment of tonsillitis and scarlet fever with oleandomycin, but the data are rather scanty and not well documented. This drug might also be expected to give good results in acute otitis media which is most often streptococcal in origin. Gagliardi (1956) found that oleandomycin, like erythromycin, was effective in eliminating *C. diphtheriæ* from the throats (or noses) of cases (19) and carriers (54) so that the length of stay in hospital was greatly reduced.

MISCELLANEOUS INFECTIONS

Poor results have been obtained, as might be expected, in intestinal infections due to Shigella or Salmonella organisms and in urinary-tract infections with the gram-negative coliform group. Cases of virus pneumonia have not responded well and presumably the drug would be ineffective in most other virus infections. It was, however, apparently used successfully in three cases of granuloma inguinale (donovanosis) by Marmell and Prigot (1957). The same authors reported cures in 34 out of 40 cases (85 per cent.) of acute gonococcal urethritis treated with 3.2 to 3.5 g. of oleandomycin over two days: only 7 out of 11 cases on a smaller dose (2.4 g.) responded.

TOXIC EFFECTS

The drug seems to be well tolerated with very few or no toxic effects. Occasional instances of nausea and vomiting and of mild diarrhœa have been reported. Because of its rather narrow bacterial spectrum, oleandomycin is unlikely to 'knock out' the normal bacterial flora in the gut although, like penicillin, it might lead to a secondary overgrowth of gram-negative coliform bacilli in the mouth. There has been no evidence experimentally or clinically of toxic effects on liver or kidney function or on the blood-forming tissues.

COMBINED THERAPY

The combined use of two antimicrobial drugs acting along different pathways may be justified (a) to prevent the emergence of drug-resistant variants as is done in the treatment of tuberculosis or (b) to obtain a synergistic effect, i.e. a bactericidal activity greater than the additive effects of the two drugs, as seems to happen with penicillin and streptomycin. On the basis of *in vitro* tests and animal experiments Jawetz and Gunnison (1953) believed that this synergistic action could occur only when two bactericidal drugs were used together but a similar effect with a bactericidal and a bacteriostatic drug, e.g. penicillin and sulphapyridine, has also been described (Ungar, 1943).

Recently, English *et al.* (1956) have reported a synergistic action, both in the test-tube and in animal experiments, with a combination of tetracycline (67 per cent.) and oleandomycin (33 per cent.) ('sigmamycin', Pfizer), as well as an inhibitory effect on the emergence of bacteria resistant to either drug. The findings, which have not yet been independently corroborated, are rather surprising in the light of Jawetz' work and it must be said that the *in vivo* experiments are not very convincing. Winton and Chessrow (1957) have claimed good clinical results with 'sigmamycin' in a variety of infections, including furunculosis, skin ulcers and genito-urinary infections. In view of the development of bacterial cross-resistance to oleandomycin, erythromycin and vancomycin, it would be unwise to use any of these three drugs together, or as an alternative treatment if the infecting organism was known to be resistant to any one of them. On the other hand, there seems to be no tendency to cross-resistance between these drugs and novobiocin, and in view of the rapid development of resistance by staphylococci to the latter drug, a combination of oleandomycin (or erythromycin) and novobiocin would be expected to inhibit the emergence of drug-resistant strains and might have a synergistic effect.

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EQUIPPING THE SURGERY

VI.—EAR, NOSE AND THROAT INSTRUMENTS

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THERE is no need for a special chair for the patient. Any dining-room type of chair will do provided there is one of similar height for the practitioner. A sterilizer, and preferably an electric one, is desirable. It is useful for the examination room to be provided with blinds or curtains: inspection of the nose, throat and ear cavities is much easier when the room is not too brightly lit. If transillumination of the nasal sinuses is to be done it is necessary to darken the room completely; the alternative method of covering the patient's and the examiner's heads with a black cloth is rather unsatisfactory. A good-sized kidney dish or two will be found useful.

Any practitioner buying instruments should deal with a reputable supplier with much experience of making good instruments. Nothing is worse than badly made, badly balanced instruments.

LIGHTING

Examination of the ear may be very satisfactorily carried out by using an electric auriscope. If, however, it is wished to carry out treatment some other form of illumination should be used. The interior of the nose can be seen only when light is projected into the cavity and, of course, if the lower pharynx and larynx are to be seen this is essential. Diagnostic sets with electrically illuminated nasal specula and laryngeal mirrors are not really practical and satisfactory. For those who have learnt to use it properly the frontal head mirror is probably best; the central hole of the mirror should be large ($\frac{3}{4}$ inch [2 cm.] in diameter) and the focal length, 8 or 9 inches (20 or 23 cm.). The mirror is best used with a special bull's-eye lamp which produces parallel rays of light, but quite satisfactory is a plain 'pearl' lamp bulb in a short lampstand or, better still, in a desk lamp with an adjustable arm. Quite useful, however, is an electric head lamp. This can be used with a dry battery and it is of course readily transportable. The lamp may be attached to a small transformer and such a piece of apparatus for both light and cautery is relatively inexpensive.

GAUZE, SPRAY AND APPLICATORS

Gauze.—Selvedge ribbon gauze ($\frac{1}{2}$ inch [12 mm.]) is often useful in the treatment of nasal and aural conditions.

Spray.—A spray for cocaine solution (Roger's crystal spray; fig. 1) will serve for introducing cocaine solution into the nose or the throat.

Applicators.—Wooden applicators 6½ inches (16.5 cm.) long are most useful for mopping out discharging ears or for use in the nose or throat. Better still is the Jobson-Horne probe (7-inch [18 cm.] with ring end; fig. 2). This instrument is very fine and may be used for mopping out the narrowest external auditory meatus. The ring end is useful for removing or loosening impacted wax in the ear. It is most useful for applying cocaine solution or ointment in the nose for any purpose and particularly for antral puncture or the removal of polypi.

FIG. 1.—Roger's crystal spray.

THE EAR

For examination of the ear the electric auriscope with specula of three or four sizes (preferably black) is excellent. Treatment of aural conditions, however, is difficult to carry out using an auriscope and it is better to use light from a forehead mirror or head light; the specula provided with the electric auriscope may be used or some separate ones obtained (e.g. Gruber's four sizes).

For the removal of wax a good metal ear syringe (Wood's) is essential. Before syringing, the impacted wax may be loosened by using the ring end of the Jobson-Horne probe or it may be softened by using 'cerumol' drops. Hydrogen peroxide (5 volumes) is sometimes used immediately before syringing. After syringing it is essential to mop the ear quite dry, using wool on wooden applicators or the Jobson-Horne probe.

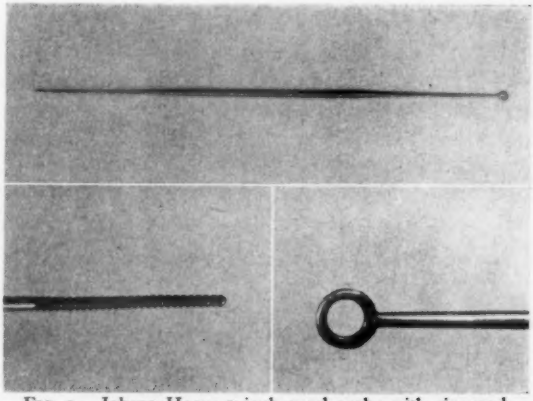

FIG. 2.—Jobson-Horne 7-inch aural probe with ring end.

A pair of very fine angled aural dressing forceps—Keen's (fig. 3) or Hartmann's (fig. 4)—are most useful for the removal of foreign bodies or for the introduction of gauze into the ear. For boils the best treatment is the introduction each day of ½-inch (13 mm.) ribbon gauze soaked in glycerin and magnesium sulphate paste (paste of magnesium sulphate B.P.C.). For severe otitis externa daily insertion of the gauze soaked in 'argyrol' (mild silver protein B.P.C.), 10 per cent. solution, is usually very satisfactory. In the treatment of chronic otitis media the clearing of all discharge by

mopping is essential. Cotton-wool wound on wooden applicators, or better still the Jobson-Horne probe, may be used to clear the meatus of all discharge. A powder insufflator is then used to blow into the ear a very little powder of boric acid containing iodine, 1 per cent.

To test the hearing (for the Rinné test) a $C^{2}512$ d.v. tuning fork is desirable, and for the testing of hearing of the higher tones the $C^{5}4096$ d.v fork; with its use the hearing loss in cases of internal ear (nerve) deafness is easily identifiable.

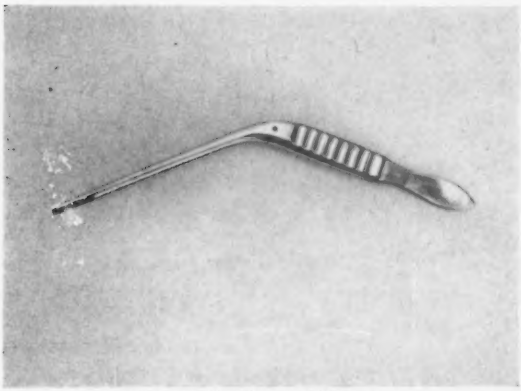

FIG. 3.—Keen's aural forceps.

Politzer's bag is helpful for the relief of deafness due to Eustachian obstruction. The difficulty is often to be sure of the exact cause of the condition. Probably the Eustachian catheter will not be used unless the practitioner has had special training in its use.

THE NOSE

Two sizes of nasal specula are necessary: a small size for children and a large size for grown-ups. Thudichum's is the best and cheapest; it is essential that the spring of the speculum should be 'right': not too strong and not too weak.

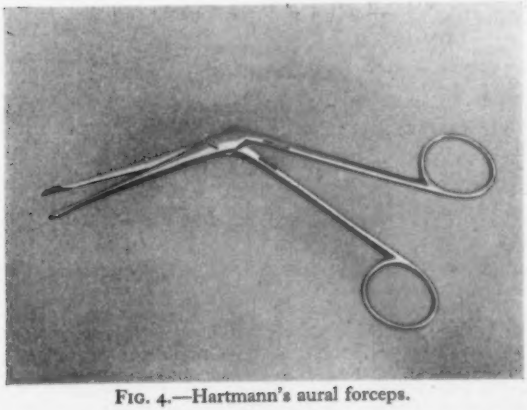

FIG. 4.—Hartmann's aural forceps.

Some form of transillumination apparatus is required for testing the translucency of the antra and the frontal sinuses. If the practitioner has a transformer it is best to have one with a handle which will take both the transillumination lamp and a cautery point.

The practitioner will often have to deal with cases of epistaxis. He will

require the Roger's crystal spray (already mentioned), a solution of cocaine hydrochloride, 10 per cent., and adrenaline hydrochloride, 1:1000 solution. Half-inch ribbon gauze soaked in a mixture of equal parts of the cocaine and adrenaline solutions may be used to plug the nose. The aural forceps already mentioned (Keen's or Hartmann's) may be used for introducing the gauze. Very useful in the nose to anæsthetize it for any purpose or to stop a bleeding vessel is the following ointment:—

Cocaine hydrochloride	120 grains (8 g.)
Desiccated suprarenal whole gland (5 in 1)	24 grains (1.5 g.)
Chlorbutol	5 grains (0.3 g.)
Liquid paraffin	220 minims (15 ml.)
White soft paraffin	to 1 ounce (30 g.)

If a bleeding point is seen it may be cauterized, using a short cautery point if a transformer is available. If the cautery cannot be used, a silver nitrate crystal may be fused to make a bead on the tip of a silver probe, or a wisp of wool wound round a wooden applicator may be used to apply a little trichloracetic acid. Useful to have available for application to the site of bleeding after cauterization is absorbent gelatin sponge B.P.C., which is obtainable in postage stamp sizes.

Unless he has had special opportunities to learn the techniques involved, the practitioner will probably not require the trocar and cannula for antral puncture and lavage, or nasal snares for the removal of nasal polypi. Hartmann's forceps may be found helpful in the removing of foreign bodies.

FIG. 5.—Lack's tongue depressor.

The pain of acute frontal or maxillary sinusitis may be relieved by spraying the nose with cocaine hydrochloride, 10 per cent. solution, to which a little adrenaline hydrochloride solution, 1:1000, has been added. Sometimes the cocaine ointment already mentioned will be painted round the middle turbinal region. Wool wound on to a Jobson-Horne probe is useful for this purpose.

THE THROAT AND LARYNX

For the throat, metal tongue depressors in two sizes (for the child and for the adult) are necessary. Lack's (fig. 5) are the simplest and most satisfactory. There should be throat swabs available in case it is thought advisable to send swabs for the culture of organisms, and also glass slides for the making of smears if microscopical examination for Vincent organisms is desired. The throat spray with cocaine solution may be used to diminish sensibility in the throat to make examination more easy or for its local anæsthetic effect. For the removal of fish bones from the tonsil a long pair of straight fine tonsil artery forceps (Birkett's) is useful. If a quinsy has to be opened

the preliminary incision through the mucous membrane may be made with any scalpel. It is useful to have a bayonet-shaped pair of fine sinus forceps (StClair Thomson; fig. 6) for opening the peritonsillar abscess. A throat brush for painting the throat may be needed. Mandl's paint and 'argyrol', 10 per cent. solution, are often used as throat paints.

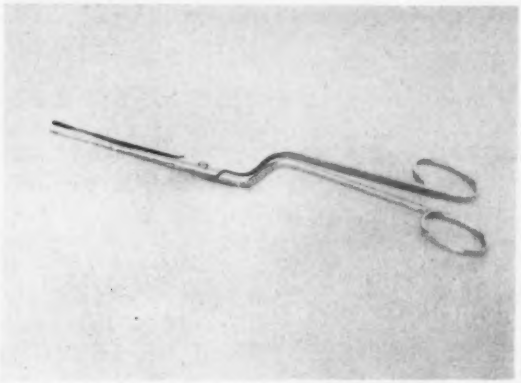

FIG. 6.—StClair Thomson's bayonet-shaped sinus forceps.

The practitioner may or may not undertake the examination of the larynx. This does require considerable skill and experience. If he wishes to do this he should have two sizes, large and small, of laryngeal mirrors. Before use the mirror must be warmed, either in the flame of a spirit lamp or in hot water. The tongue is held out by gripping it with a piece of gauze (special tongue cloths are not necessary). With the laryngeal mirror, not only the larynx but the base of the tongue, the lower part of the pharynx, and the pyriform fossæ are examined. In some patients examination is very difficult and unless the practitioner has really learnt the technique thoroughly it is probably best that he should refer the case for specialist examination. If he cannot see the whole region satisfactorily and well, it is important that he should do this without delay, if symptoms indicate disease which he cannot locate by his examination.

THE NASOPHARYNX

The nasopharynx is the most difficult of the various nose and throat regions to see well. This examination should be undertaken only if training has made for experience. Two sizes of post-nasal mirror, large and small, are required.

REVISION CORNER

PICA

PICA is generally defined as a perversion of appetite in young children up to the age of three years. Appetite for normal foods is impaired and the common food substitutes preferred by the child are sand, earth, grass, plants from the garden, blanket wool, hair from the head, paint from furni-

ture or toys, coal, ashes, plaster from walls or even animal droppings. The child usually craves one or two such substances—usually those to which he has easy access. Parents of such children are often astonished at the ingenuity and pertinacity of the toddler of two or three years as he overcomes the obstacles placed between him and the object he desires.

ETIOLOGY

The origin of this habit is often doubtful, but it is important to remember that it is with the lips that infants explore the shape and texture of objects as well as their taste. In most children in whom pica is a symptom, however, there is a general nutritional upset with ample evidence of faulty digestion and unhealthy bowel action. There is often present, or a history of past, infestation with threadworms, roundworms or tapeworms. The children are often classified as nervous and, in those in whom the habit persists into later childhood, there are other reasons to suspect neurotic tendencies or mental deficiency. Such, however, is not always the case, for recently, while questioning a mother about her child's perverted appetite, she said that she did not regard that as very important for she herself, aged about thirty, had 'always been partial to a bit of plaster' till a few years before! Apart from that admission she had seemed to be a normal sensible parent.

The attitude of parents to pica in their children is very variable. The ultra-hygienic 'everything sterilized' type will be horrified at the least experiment in chewing, whilst the more tolerant mother of many will only be stimulated to action by some gross departure from normal, as in the case of the mother who said: 'I didn't mind her eating old newspapers but when she ate three pound notes from the table I knew it was time she saw a doctor'! Alas, not even the doctor could bring them back in negotiable form.

DANGERS

There are, of course, dangers attached to the habit. In addition to the obvious dangers of swallowing harmful foreign bodies, such as broken glass, and the increasingly obstructive effects of a hair ball in the stomach, a more insidious danger is that of lead poisoning. Fortunately, the law supports the use of lead-free paint for furniture, toys and all indoor paintwork, but in these days of 'do-it-yourself', it may appear to some fathers a shame to waste the paint left over from the garden seat when it might be used to touch up some indoor woodwork. What therefore may start as a pleasant exercise for growing teeth may end as a prolonged debilitating illness or even a death-dealing lead encephalopathy.

MANAGEMENT

In the management of the case of a child with pica as a main symptom it is necessary to remember that the treatment of the underlying nutritional disturbance and gastro-intestinal ill health is often of greater importance

than measures to prevent satisfaction of the perverted appetite. For this last object the parents must keep the offensive substances out of reach and sight of the child if possible, although in the case of earth, grass, plants, and the like, careful supervision when outdoors will be necessary and the deflection of the child's attention to more normal play when temptation becomes too great.

Careful examination is necessary to determine local irritation of the mouth or teeth, presence of worm infestation or any degree of anæmia, and the appropriate treatment given. Constipation should be overcome and a low-residue type of diet should be instituted. Many of these young children are achlorhydric and the use of dilute hydrochloric acid, 5 minims (0.3 ml.) in water before and again during each meal, is useful as a temporary measure until the almost inevitable mucous gastritis is overcome and normal gastric secretion is resumed. Full vitamin intake should be assured with especial emphasis on vitamin B. The nervous instability in many of these children should be understood by the parents who, by reducing fuss and excitement in the home background to a minimum, and by keeping the family routine as regular as possible, will do much to reduce the tensions and frustrations which are present as cause or effect of some perversions of appetite. Lastly, the breaking of a bad habit in childhood, which entails separation of the child from something he craves, demands an extra demonstration of love and security, the lack of which in the past may indeed have been a factor in maintaining such an abnormal symptom.

PROGNOSIS

The long-term outlook is good although the tendency to relapse is present for months. For young children life is full and exciting; new experiences occur daily and in a well-adjusted family bad habits can more easily be replaced by good habits. Realizing that, it is only for the doctor to remove the obvious faults and wait for his great helpmeet, Nature, to complete the cure.

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DYSARTHRIA

'Articulation is the motor function whereby words, formulated in the brain, are converted into sounds' (Russell Brain, 1955).

DYSARTHRIA is a disorder of articulation. The recognition of this symptom may be a matter of some difficulty, for patients and their relatives often fail to remark the disorder themselves and consequently do not complain of it. Further, standards of articulation vary widely according to the place of

origin and standard of education and intelligence of the patient. Speech which might be regarded as clear for a Cockney would be grossly dysarthric in a newsreader. I have found in Metropolitan practice that the approach of Shaw's Professor Higgins is rewarding, routine attention to the patient's accent leading to the early diagnosis of dysarthria. Aphonia is a disorder of phonation, or sounding and pitching of the voice. Dysphonia and dysarthria may coexist in many neurological conditions; therefore both disorders are considered here. Lack of space precludes a discussion of dysarthria in children, a subject on its own, or of stuttering, a disturbance of articulation not caused by organic disease.

LARYNGEAL DISEASE

Disease of the larynx, or of its neuromuscular apparatus, produces hoarseness. This symptom is commonly due to local conditions: acute or chronic laryngitis. Traumatic laryngitis is sometimes encountered in patients whose work involves much speaking or singing. Benign and malignant tumours of the larynx may present with hoarseness. Functional aphonia is a painless condition in which the patient speaks in a whisper; it is easily recognized because the ability to cough is retained. Laryngeal paralysis results from lesions of the nucleus ambiguus, in the medulla, or of the vagus nerves. It may occur as a symptom of poliomyelitis or vascular disease of the brainstem; rarer central neurological causes include syringobulbia and neoplasms of the medulla. Peripheral affections of the vagi or recurrent laryngeal nerves at any point in their courses may lead to hoarseness, trauma and compression from neoplasm being the commonest pathological mechanisms. The hoarseness caused by a mild attack of bulbar poliomyelitis may be dismissed as due to a common cold; the disturbance of voice production is associated with some degree of dysphagia and consequent pooling of secretions in the pharynx; confusion should not arise if history and examination are careful. Diphtheritic neuritis must now be a very rare cause of laryngeal palsy. Laryngeal examination is required in the patient whose hoarseness is persistent.

Proper function of the musculature of the lips, jaws, tongue, palate and larynx and of the muscles of respiration is required for articulation. The teeth and hard palate also play an important part. The sinuses are concerned with the quality of the voice. If a local condition produces dysarthria the cause is usually obvious, but I have had patients with carcinoma of the tongue, mouth and nasopharynx referred to me for neurological opinion on account of their speech disturbance. Routine examination of the mouth and throat precludes mistakes of this sort.

THE PHYSIOLOGY OF ARTICULATION

The physiology of articulation can easily be revised by repetition of the alphabet and common consonantal linkages. Articulation and phonation require bilateral movements of the muscles concerned. Briefly, the neuro-

anatomical substrate is as follows. Fibres arise in the lower part of the left pre-central convolution of the brain in a right-handed person, and cross in the corpus callosum to the corresponding part of the opposite hemisphere. From each side fibres descend in the pyramidal tracts to the relevant motor cranial nerve nuclei in the brain-stem. These pathways, together with extra-pyramidal and cerebellar linkages, are concerned with the initiation and co-ordination of the movements required for speech. When dysarthria is due to organic nervous disease the history usually brings out other symptoms helpful to the physician, and we have already seen that the disorder is more often a sign than a symptom.

NEUROLOGICAL CAUSES

It will be clear from this brief account of the anatomy of speech production that a wide range of neurological disorders may cause dysarthria. A slurring dysarthria occurs in patients with frontal lobe lesions, especially of degenerative, inflammatory or toxic type. Common examples include cerebral vascular disease, cortical atrophy and alcoholism; rarer causes include neurosyphilis, tumour and head injury. The dysarthria of the punch-drunk boxer is a prominent symptom. Bilateral affections of the pyramidal tracts, for example cerebro-vascular disease and motor neurone disease, cause a spastic weakness of the muscles of articulation and phonation. The voice here is slurred and indistinct; whilst the normal melodic line is lost at an early stage, variations in pitch of an uncontrolled variety may be remarkable for some time. Both paralysis agitans and post-encephalitic Parkinsonism cause a slurring, monotonous dysarthria by their effect on the extra-pyramidal system. With chorea, however, there is a jerky and explosive manner of speaking. The ataxic speech of cerebellar disease is easily recognized, and it is usually associated with other clear indications of cerebellar dysfunction. Multiple sclerosis is the common cause of this form of dysarthria.

A disease process affecting the lower motor neurones at any point from the brain-stem motor nuclei to the motor end-plate will cause dysarthria, the exact variety depending upon the nerve or nerves involved. Acute central lesions operating in this way include occlusive states of the vertebral and basilar arteries, and their branches, and poliomyelitis. The vascular conditions are seldom difficult to recognize; other symptoms and signs are present to help. Poliomyelitis may be missed, and it is a diagnosis which should come to mind in the examination of a patient with an acute bulbar palsy, whether mild or severe. More chronic central disorders include motor neurone disease, a relatively common neurological condition. Here the muscular weakness is often, though not always, due to combined upper and lower motor neurone lesions; consequently, local signs in the early stages may be limited to reduced mobility of the tongue and a brisk jaw jerk, plus the dysarthria; fasciculation and atrophy of the tongue follow. Syringobulbia and neoplasm are much rarer causes of dysarthria.

The cranial nerves may be affected by a generalized peripheral neuro-

pathy, especially of the Guillain-Barré type. When this happens dysarthria and dysphagia are added to the weakness of limbs and trunk. Occasionally the illness begins with bulbar symptoms. This form of neuropathy is important to recognize, as respiratory weakness and bulbar palsy can cause death if not properly treated. Diphtheria is no longer an important cause of palatal palsy in this country.

DISEASES OF THE MUSCLES

Lastly, articulation may be faulty as a result of disease in the muscles. Myasthenia gravis may present with fluctuant weakness of the voice. This condition may arise at any age, but it is particularly frequent in young women, who may be thought to be suffering from hysteria. The history should suggest the diagnosis. Primary muscle diseases responsible for dysarthria are dystrophia myotonica, polymyositis and carcinomatous myopathy. Dystrophia myotonica, and other muscular dystrophies, are easily recognized. Polymyositis is more difficult to diagnose, but usually skin rashes are present at some stage in the course of the disease. Finally, there is a rare but interesting group of patients with myopathy associated with carcinoma of the lung.

SUMMARY

The diagnosis of the cause of dysarthria is a good deal less difficult than might be surmised from the foregoing paragraphs. Once the symptom is recognized and analysed, the underlying disease process can usually be sought out by a careful clinical approach.

R. A. HENSON, M.D., F.R.C.P.
Assistant Physician, and Neurologist, The London Hospital.

NOTES AND QUERIES

Fallot's Tetralogy

QUERY.—I should be grateful for an expert opinion in connexion with the prognosis of Fallot's tetralogy. The patient in question, aged seven, is undersized but mentally very well up to standard. He has a perceptible 'bluish' tinge at rest; is definitely blue on exertion, and has a tendency to recurrent bronchitis. I am particularly interested in his chances of reaching adult life and in what state he is likely to be if he does reach such an age. He is going to be investigated from the cardiac surgery point of view when his 'appointment turn' comes round. If they can do anything for him, I am wondering if it is known how this will influence the prognosis from the long-term point of view.

REPLY.—In answering this question it is assumed that the diagnosis of Fallot's tetralogy is reasonably certain: that is to say, that there is a combination of pulmonary stenosis, high ventricular septal defect, and over-riding of the aorta. It will be appreciated that each of these anomalies varies in degree, and the prognosis for the individual patient will depend upon the precise anatomy of the malformations. All-important is the severity of the pulmonary stenosis. In general it can be said that, although a mild case might live to middle life, probably less than 10% of infants with Fallot's tetralogy survive beyond the age of 20, and by this age

most children will succumb to intercurrent infection, bacterial endocarditis, cerebral thrombosis, cerebral abscess, or, less frequently, cardiac failure. The severity of symptoms and the degree of underdevelopment will give some guide as to the over-all severity of the condition. From the hæmodynamic point of view the important factor is the degree of shunting from the right ventricle into the aorta, with consequent decrease in pulmonary blood flow. Central cyanosis from oxygen unsaturation of the arterial blood will be reflected in compensatory polycythæmia and this, too, is a useful guide to severity. Although the pattern of right ventricular hypertrophy is usually present in the electrocardiogram in this condition, this is a less useful guide than in pulmonary stenosis with a normal aortic root.

It will be apparent that the prognosis for a child of 7 can be roughly assessed from the symptoms, the degree of physical retardation and of central cyanosis, together with the radiological evidence of cardiac enlargement and pulmonary avascularity and electrocardiographic evidence of right ventricular hypertrophy. If the condition is of moderate severity now and the child does reach adult life he is likely to be severely handicapped.

Surgical treatment has only been available for about ten years and the results are most encouraging, but naturally no information about the long-term outlook is yet available.

R. W. D. TURNER, O.B.E., M.D., F.R.C.P.

Morphine in Congestive Heart Failure

QUERY.—I would appreciate advice on the use of morphine in the dyspnœa of heart disease. It is generally accepted that morphine is the drug of choice in acute left heart failure, but for the dyspnœa (especially nocturnal) of congestive cardiac failure (right heart failure) secondary to, say, rheumatic heart disease with mitral valve involvement predominating many hesitate to use morphine. Is morphine contraindicated in congestive cardiac failure and if so why?

REPLY.—Morphine is not contraindicated in congestive heart failure. It is certainly the drug of choice in acute left ventricular failure, and in the early stages of treatment for bilateral heart failure it is useful to secure sleep and allay anxiety. It must be emphasized, however, that the basic treatment for the insomnia, dyspnœa, dyspepsia and lassitude of congestive heart failure lies in the treatment of heart failure by the proper use of digitalis glycosides and mercurial diuretics.

Morphine is contraindicated in congestive heart failure due to lung disease; clearly the suppression of respiration by morphine increases the anoxia which in cor pulmonale is the main cause of the heart failure.

WALLACE BRIGDEN, M.D., F.R.C.P.

Excessive Salivation in Infants

QUERY (from a reader in Iraq).—I should be grateful for information about the causes of increased salivation, especially in infants and children. I have noticed, in cases of children and infants, that the only physical finding is tonsillitis. In infants I have also noticed increased salivation in those who are not given plain water for drinking for the first three to six months after birth. The tradition among natives (where I serve as a district physician in a dispensary) is not to give water to infants for three to six months! As I have no laboratory aids for further investigation, I should like to know the causes of increased salivation, and its treatment.

REPLY.—The young infant does not secrete much saliva because many of the salivary gland cells do not mature until the age of 3 to 6 months. About this age the flow of saliva is increased and drooling occurs because the child has not learned to swallow it. Excessive secretion of saliva in children is often produced reflexly by the irritation of teething or lesions in the mouth, such as herpetic stomatitis and tonsillitis. Mercurial compounds, which were formerly incorporated in most teething powders until their possible role in the causation of chronic nephritis and pink disease was suspected, may also cause it. So, too, may certain cerebral disorders, such as encephalitis and chorea.

The tradition among natives not to give water to infants in the first 3 to 6 months of life is most commendable, because the risk of introducing organisms which might cause gastroenteritis is thereby greatly diminished.

The treatment of excessive salivation consists essentially in accurate diagnosis of the cause and its removal. Symptomatic relief with parasympathetic inhibitors, such as atropine derivatives, is seldom justifiable except in connexion with anæsthesia and surgical procedures, but salivation can be reduced over a period by the use of less toxic derivatives such as atropine methonitrate, used in the medicinal treatment of pyloric stenosis in infancy. This alkaloid can be given to infants most conveniently in tablet form (1/60 gr. [1 mg.]) or alcoholic solution (0.6% in 90% alcohol). Three minims of this solution contain 1/60 gr. (1 mg.). Both of these preparations are issued by Bayer Products as

'eumydrin'. In infancy one such tablet is placed sublingually, where it is rapidly dissolved and absorbed; or two or three minims (0.1 or 0.2 ml.) of the alcoholic solution are dropped on the tongue, where absorption is also rapid. It is administered three or four times a day.

PROFESSOR J. L. HENDERSON, M.D., F.R.C.P.

Metallic Taste

QUERY.—Can you explain why certain patients complain of a metallic taste and are otherwise apparently healthy? I have a woman patient aged sixty, who has had this complaint for about a year. She has had her teeth checked regularly by a dentist and has no other physical signs. The taste does not respond to any medicines I have given her, nor is it any different when not taking medicine. Is there any cure for this condition?

REPLY.—These patients present a considerable problem, and sometimes no satisfactory conclusion is reached. The metallic taste is probably a complex of sweet and sour tastes and may be related to stimulation of olfactory receptors. Local causes include antral infection, the presence of nasal polypi, and lesions of the salivary glands. The teeth should be re-examined to exclude the possibility of electro-galvanic discharge between dissimilar dental fillings. Where dentures are worn, undue stress may be thrown on the temporo-mandibular articulation; relief is obtained by building up the denture to restore the line of 'bite'.

Such upset of taste may be an early indication of the development of pernicious anæmia, sprue or pellagra, and special inquiry should therefore be made about diarrhœa, weakness of the legs and adequacy of the diet. It may also be encountered with cerebral lesions, particularly thrombosis of a small vessel in the temporal lobe or uncus; the classical onset—sudden, with giddiness and nausea—is by no means constant.

Mouth washes, a sedative, nicotinic acid or tolazoline may be helpful, and old-fashioned remedies such as sucking an acid drop or eating a small quantity of raw parsley are worth a trial.

J. RONALD, M.D., F.R.C.P.ED.

'*Lipstick Dermatitis*'

QUERY.—A patient of mine suffers from severe cracking of the lips whenever she uses a lipstick. Lanolin cures the condition but she is anxious to use a lipstick. Could you suggest a formula which would not cause the trouble?

REPLY.—The severe cracking of the lips is almost certainly the sign of a contact sensitization dermatitis from the lipstick. The colouring dye, eosin, is usually the irritant concerned and exposure to sunlight may precipitate or accentuate reaction, as this chemical causes photosensitization.

A change of lipstick may lead to cure and most sufferers can tolerate an eosin-free lipstick now marketed by many of the cosmetic firms. Occasionally other ingredients, such as perfume or the actual constituents of the stick, may irritate, and cosmetic firms will then often supply the various ingredients for patch testing, so that a non-irritating lipstick may be made. Theatrical rouges or lakes can be substituted for lipsticks. The acute attacks of cheilitis are most easily suppressed with 1% hydrocortisone ointment.

GEOFFREY HODGSON, M.B.E., M.D.

Earthworm or Roundworm?

QUERY.—A few days ago a child's mother brought a dead earthworm along to the surgery, stating that her child had passed this 8-inch (20 cm.) worm per rectum into her 'pottie'. My reassurance that the perfectly normal-looking worm in the bottle would have been digested and that her statement could not be true was not appreciated. This is undoubtedly the case, is it not?

REPLY.—My opinion on this query is that the child's mother made a true statement and that the 'earthworm' was in reality a specimen of the common roundworm of man, *Ascaris lumbricoides*. It is by no means uncommon for children to harbour this parasite and to pass one occasionally as described. I suggest that the specimen, if it has been preserved, be re-examined carefully by a helminthologist.

PROFESSOR J. J. C. BUCKLEY, D.SC.

Ferrous Gluconate

DR. W. M. DAVIDSON writes:—In discussing oral iron in my article on 'Anæmia in Pregnancy' (*The Practitioner*, 1957, **178**, 161) I made the following statement: 'Ferrous gluconate, 100 milligrams (three tablets) a day, gives good responses' (p. 165). This statement seems to have given rise to some misunderstanding. This has arisen from the fact that we always think in terms of the iron content of a preparation and rather forget the inert vehicle. Ferrous gluconate tablets B.P.C. contain 300 mg. of ferrous gluconate, of which 34 mg. is elemental iron. This means that one tablet of ferrous gluconate B.P.C. thrice daily gives approximately 100 mg. of elemental iron, the only material of interest in this connexion.

PRACTICAL NOTES

Oral Therapy in Pernicious Anæmia

'ORAL preparations of vitamin B_{12} and intrinsic factor are quite unsuitable for routine use in the maintenance treatment of pernicious anæmia', according to J. F. Adams of the Royal Infirmary, Glasgow (*Scottish Medical Journal*, April 1957, **2**, 151). The preparation used in the trial upon which this conclusion is based was 'a well-known preparation marketed in Great Britain, each tablet said to contain 7.5 μg. of cyanocobalamin and the extract of 1.5 g. of hog stomach mucosa'. Of the 73 patients in the trial, 58 who had previously been maintained on parenteral cyanocobalamin received one tablet daily, whilst 15 seen in relapse received initial treatment with the oral preparation and were than maintained on one tablet (12 patients) or two tablets (3 patients) daily. After a period ranging from sixteen to thirty-six months the results were found to be unsatisfactory in 35 cases (48%). It is noted that, in spite of the fact that the patients were seen at least every four weeks, in nine cases 'red cell counts of 3 million or less were reached before they could be restored to higher levels by appropriate treatment'.

Busulphan in Chronic Leukæmia

BUSULPHAN ('myleran'; 1:4-dimethanesulphonyloxybutane) 'does not seem to prolong life in chronic granulocytic leukæmia' but 'is as effective as radiotherapy in controlling the disease', according to Dag Turesson, of Gothenberg (*British Journal of Hæmatology*, April 1957, **3**, 220). This conclusion is based upon the findings in a series of 39 cases, 19 of whom have died since busulphan therapy was started in October 1952. This gives an average duration of the disease of 27.5 months, compared with 26.5 months in 28 patients observed before busulphan was introduced. Initial doses of the order of 0.06 mg. per kg. body weight brought the leucocyte count to normal levels within two to eight weeks; thereafter the count was kept within the normal range by maintenance doses of 2 mg. a week to 4 mg. a day. The spleen usually became impalpable about two weeks later. Those patients with many myeloblasts in the circulating blood and sternal marrow did not respond well to treatment. Most patients were treated throughout as outpatients, and the majority were able to resume work after one to two months. Few toxic effects were noted: thrombocytopenia developed in two patients, with a fatal outcome in one. Several of the young women patients developed a persisting amenorrhœa.

Prognosis in Congenital Aortic Stenosis

IN a series of 73 patients with congenital aortic stenosis, all of whom were under 16 years of age when first seen, I. B. Braverman and S. Gibson (*American Heart Journal*, April 1957, **53**, 487) report a mortality rate of 8.2%. Of the six patients who have died, five died suddenly but, with the possible exception of one boy who was playing ball, none of the patients died while overexerting himself. All six who died were under the age of 16 years. Three of the six patients who died experienced at least one syncopal attack before the fatal one. Forty-one of the patients were completely asymptomatic, and 26 had one or more symptoms. Easy fatiguableness was the most common symptom, occurring in nine patients; six complained of headaches, four of spells of dizziness, and four of shortness of breath on exertion. Nose-bleeds occurred in four. Many of the asymptomatic patients were very active. Thus, one young man, who is now 18 years old, played football, whilst another, aged 19½ years, can play 36 holes of golf a day. The authors consider that selected cases should be considered for aortic valvulotomy, the principal indications for surgery being the occurrence of syncope and easy fatiguableness, cardiac enlargement, and marked left heart strain. No restriction is recommended on the activities of asymptomatic cases, except to discourage competitive sports. Neither should parents be told of the possibility of sudden death in those who have no symptoms: 'They would then live in a state of constant, helpless fear'.

Viomycin in Pulmonary Tuberculosis

VIOMYCIN is 'a useful and reasonably safe agent for operative cover' in patients who 'carry organisms moderately or completely resistant to at least two of the three standard antituberculosis agents', according to J. R. Edge and his colleagues (*British Journal of Tuberculosis and Diseases of the Chest*, April 1957, **51**, 168). This conclusion is based upon their experience with 36 consecutive such patients, all of whom, in spite of having been on antibacterial treatment for long periods, remained sputum positive. Twenty-five were submitted to resection, and 11 to thoracoplasty, under cover of viomycin in combination with whatever other agent or agents appeared most suitable. The dosage of viomycin was 2 g. (1 g. morning and evening) twice weekly, for an average period of twenty-three weeks. Apart from one patient who developed contralateral spread of the disease

following resection, no serious operative complications were encountered, and no patient developed a broncho-pleural fistula. The drug had to be withdrawn in two patients because of side-effects—one on account of severe bronchospasm, and one on account of generalized erythema with facial œdema. In two others dosage had to be reduced—on account of bronchospasm and of severe conjunctivitis.

Chronic Alcoholism and Parotid Enlargement

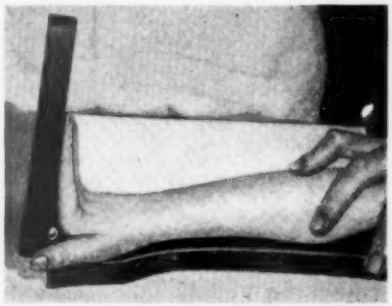
CONFIRMATION of continental reports that asymptomatic enlargement of the parotid glands is often found in patients with chronic alcoholism is adduced by S. J. Wolfe and his colleagues (*New England Journal of Medicine*, March 14, 1957, **256**, 491). They report a series of 16 patients with hepatic cirrhosis associated with chronic alcoholism who had bilateral, symmetrical parotid swelling. The glands had a firm rubbery consistence; they were neither tender nor inflamed, and the overlying skin was freely movable. The ages of the patients ranged from 29 to 67. Ten of them died, nine from hepatic failure with severe icterus. In those who survived, rapid improvement in liver function was accompanied by diminution in parotid size. None of the patients was aware of the enlargement of the glands, and there were no complaints of dry mouth, excessive salivation or local pain. The pathogenesis of parotid hypertrophy in such cases is unexplained, but it is suggested that it may be related to the enlargement that has been reported in malnourished individuals.

Aminopterin as an Abortifacient

THE abortifacient properties of the folic acid antagonists is well recognized, and aminopterin has actually been used to produce therapeutic abortion in the United States. So well are these properties now known on the other side of the Atlantic that apparently aminopterin is now known among the public as 'these abortion pills'. F. Munroe Bourne and his colleagues (*Canadian Medical Association Journal*, March 15, 1957, **76**, 473) now report what they believe to be the first case of poisoning due to unauthorized use of aminopterin as an abortifacient. The patient was the 44-year-old mother of four grown children, who having missed one period, 'began to fear that she might be pregnant'. On the advice of a friend she bought some aminopterin tablets at a 'neighbourhood druggist'. Three days later she was admitted to hospital on account of stomatitis, gingivitis, laryngitis and a macular eruption of the skin. She subsequently developed an extensive dermatitis and aborted. On the day of discharge from hospital, fourteen days after admission, her hair began to fall out and two weeks later she had lost 75% of her hair. It eventually grew again. Treatment consisted of citrovorum factor and penicillin. The amount of aminopterin consumed was never determined accurately, but was between 10 and 17 mg.

Hyperextensive Fingers in Rheumatic Children

CONFIRMATION of the clinical observation that rheumatic children have a characteristic type of hand, the feature of which is hyperextensibility of the fingers, is reported by Umberto Callegarini (*Bulletin of St. Francis Hospital and Sanatorium*, January 1957, **14**, 32). A comparison of 135 rheumatic children and 135 control children, aged 4 to 16 years, showed that the majority of the rheumatic children had 'a marked mobility of the metacarpophalangeal joints and



that the fingers could be extended to 90 degrees and over (see figure), easily and smoothly without producing pain'. Only a few of the control group showed a high degree of extensibility. In more than 60% of the rheumatic children a dark line was noted above the interphalangeal joints. The difference in degree of extensibility between the rheumatic and control groups was present at all ages, and ranged from 11 to 15 degrees, with a tendency to increase after the age of twelve.

Mepacrine and Tapeworm Infestation

'THE virtual absence of adverse effects and a failure rate of only 9% on review three months after treatment indicates that the use of mepacrine for mass treatment of tæniasis with suitable adjustment of dosage for children and the chronic sick, is safe and relatively effective and that by this method of treatment it should be possible to reduce tapeworm infestation in a

community to a negligible proportion', according to J. A. McKinnon (*East African Medical Journal*, January 1957, **34**, 15). The course of treatment consisted of an initial dose of 480 grains (32 g.) of magnesium sulphate 'on an empty stomach'. All men whose stools contained visible segments or ova were then given 800 mg. of mepacrine by mouth in four equally divided doses at five-minute intervals, with sips of an antacid mixture to prevent nausea and vomiting between doses. One hour after the last dose of mepacrine, 960 grains (64 g.) of magnesium sulphate were given by mouth. Of the 494 men, aged 16 to 45, so treated, 42 had visible segments, and 70 had ova, in their stools on the fourth day: a failure rate of 22.67%. Three months later, 200 men were still available for examination, and the failure rate among them was 9%. It is stressed that if this method was used in a field campaign, it would be necessary to adjust dosage for children, and for adults who were not in a good state of health and nutrition.

Chlorpromazine in Leprosy

As a result of his experience with 31 patients suffering from one or more of the painful complications of leprosy, K. Ramanujam (*Leprosy Review*, April 1957, **28**, 60) concludes that chlorpromazine is of value as a pain-relieving agent. The series consisted of 21 patients with neuritis, three with joint pains, two with neuritis and joint pains, and five with generalized body pain. The previous routine treatment of these painful complications had been the intravenous administration of potassium antimony tartrate, 0.02 g. daily for three days, followed by 0.04 g. for the next three days. In addition, the patients were given sodium salicylate orally. The results of such therapy had been 'uniformly good'. In the present investigation the patients were given 25 mg. of chlorpromazine orally two or three times daily, and 25 mg. of promethazine at night. In addition, they were given sodium salicylate thrice daily. If the response was not satisfactory, or initially in cases with very severe pain, potassium antimony tartrate was given intravenously and chlorpromazine orally. It was found that the chlorpromazine regime was effective in the majority of cases with mild or moderate pain. The combined potassium antimony tartrate and chlorpromazine regime gave 'better and quicker results' than potassium antimony tartrate alone. No side-effects of chlorpromazine were encountered.

Diaper Dermatitis

SATISFACTORY results are reported by H. W. Kaessler (*Archives of Pediatrics*, February 1957, **74**, 47) from the use of a silicone-containing powder in the treatment of diaper dermatitis. The preparation he used is known as 'baby silicare powder' and contains silicones, glyoxyl diureide and hexachlorophene in a fine talc base. The efficacy of the preparation is attributed to 'the ability of silicone to repel moisture; the stability, and non-irritant keratolytic qualities of diureide of glyoxilic acid which stimulates epithelial healing; and the effective and non-sensitizing bacteriostatic attributes of hexachlorophene'. All of 84 severe cases of diaper rash cleared following the use of the powder, compared with 81% of a control group of 42 cases. In a further group of 127 infants in a home for mentally retarded infants, the powder was used prophylactically and prevented inflammation in over 80% of cases. No side-effects were noted, and in more than 200 patch tests there were no positive reactions. It is suggested that bedridden incontinent patients of all ages, 'exposed for a sufficient length of time to irritation from ammonia produced by the action of bacteria on urinary area, are likely to benefit' from this preparation.

Ornithosis in Pigeons

ABOUT 50% of the street pigeons of Oslo have been found to be infected by ornithosis according to J. C. Ulstrup and Chr. Neess (*Journal of the Oslo City Hospitals*, March 1957, **7**, 33). Of 62 pigeons shot in Oslo, 32 (52%) were found to harbour antibodies against ornithosis antigen prepared from the parakeet strain of ornithosis virus isolated in Albany in 1952, when tested with the direct complement fixation test. The view is expressed that, although it is difficult to tell to what extent pigeons are infective for man and a hazard to the human population, 'it is not unlikely that many "virus pneumonias" and possibly inapparent infections by humans may be caused by infection from pigeons'.

Dental Hæmorrhage

THE use of the vitamin K preparation, 'synkavit', is recommended by S. H. Partridge (*British Dental Journal*, April 2, 1957, **102**, 274) for the prevention of dental hæmorrhage. He prescribes 30 mg. a day for six days, starting four days before the extractions are due to be made. For the last nine years he has used this procedure in all cases with a history of post-operative bleeding, and has had only one failure. He reports one case in which, without 'synkavit' cover, 10 loose teeth were extracted under nitrous oxide anæsthesia, and every socket had to be treated for profuse bleeding. Subsequently, another 10 teeth were removed, following the use of vitamin K, and in no case was there any abnormal bleeding.

REVIEWS OF BOOKS

Battle for the Mind. By WILLIAM SARGANT, M.B., F.R.C.P., D.P.M. London: William Heinemann Ltd., 1957. Pp. xv and 248. Figures 24. Price 25*s*.

THIS is an important book and may become a classic, important for doctors, lawyers, politicians, priests, penal reformers, and indeed for all the more active globules of the intellectual cream. The Newton-apple incident, the genesis of the book, was when the author, a psychiatrist, came home during the last War to his father's manse, picked up John Wesley's Journal for 1739-40, and realized that what John Wesley had been doing two hundred years before, producing emotional excitement, often leading to emotional collapse, by vigorous minatory preaching, and then implanting his own beliefs and patterns for behaviour on washed minds, was precisely what he himself had been doing with the victims of severe battle and bombing stress by making them live again through their own or even imagined experiences, and then on purged minds planting the seeds of sanity. The various patterns of mental breakdown from, or of adaptation to, severe stress were elucidated by Pavlov with dogs and this work forms the basis of the book, for elaboration into the more intricate responses in human beings. The thesis is that the primary mechanism is the same in abreactive techniques, religious conversion, political indoctrination, and shock treatments such as E.C.T.—by severe and/or prolonged stress the mind becomes like a clean slate on which new beliefs can be chalked. The initial process is assisted by tension, uncertainty, bodily weakness from starvation, fasting, lack of sleep, illness or operation, and by torture, 'beating-up' and fear.

The book induces the same feeling of horror as did Orwell's 'Nineteen-eighty-four', but it is a more lingering horror because it is factual and shows how even the most intellectual and strong-willed can have their beliefs and principles changed by adopting certain methods; only the abnormal, the psychotics and grossly defectives can escape. The chapter on 'The Eliciting of Confessions' contains cautionary tales for psycho-analysts, policemen and Home Secretaries. There are eight pages showing that in all probability the series of confessions by Timothy Evans, who could neither read nor write and was hanged for murder largely on the evidence of the multi-murderer Christie, were obtained by suggestive questioning by the police when he was in a state of emotional collapse from fear.

The author draws from a wide field—anthropology, Calvinistic and Quaker techniques of conversion, modern snake-handling, Christian groups in Tennessee, the Rock and Roll crazes, police methods behind the Iron Curtain under Stalin from the personal experiences of their victims, Bantu Christian pastors who make their converts dream stereotyped dreams, Billy Graham, the Voodoo cult, and some deplorable activities of United States police forces with 'lie detectors': all the brain-washed and brain-washing world is his oyster.

An interesting interpolation is a chapter on 'Brain-washing in Ancient Times' by Robert Graves. There is no new material in this book, it is a masterly selection of known facts and a brilliant synthesis of them. The style is crystal clear and, except possibly for the Pavlovian terminology, or rather its not too happy translation, makes easy reading for any layman; it is written with a disarming yet assertive humility. In the present turmoil of world creeds and systems of thought it is almost essential reading for the intelligent.

Dimly ahead one can sense there may be an even more embracing synthesis, which will link all this mainly individual matter with social function; the necessity for each group of the gregarious animal, man, to work in emotional unison, with its survival value, for an emotionally united though possibly a deluded group, other values being equal, will beat the emotionally divided group every time; a synthesis which will link the mass migrations of history to modern nationalisms, and possibly explain the mechanisms involved by the principle of regression. It is not the least part of Dr. Sargant's art that he stimulates conjecture.

Operative Surgery, Vol. 3. Edited by CHARLES ROB, *M.C.*, M.CHIR., F.R.C.S., and RODNEY SMITH, M.S., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1957. Pp. 215. Illustrated. Price £5 10*s*.

THIS volume completes the 'surgery of the rectum and anus', and deals for the most part with thoracic surgery. As in the first two volumes, the production of the book is excellent, the chapters are written by experts in their particular subjects, and the illustrations are by the best medical illustrators. Again as in the former volumes, this one is based on the premise that surgery can be taught by pictures. Each chapter is by two experts, with a different training and speaking a different language, and the result, while for the most part better than in the early volumes is unnecessarily confusing.

The last section deals with Heller's operation

for achalasia. The crucial illustration, no. 3, shows an incision of the wrong size at the wrong level in an œsophagus that is not affected by achalasia. In the section on intrathoracic goitre, fig. 5 shows the inferior thyroid artery as a branch of the common carotid. In the section on mediastinal tumours, fig. 1 shows the 3rd, 4th and 5th ribs in contact, with no intercostal spaces. Figure 10 in mitral valvotomy is unintelligible without some caption. The same applies to fig. 3 in pulmonary valvotomy. Fig. 5 and 6 in pericardiectomy are not surgical, but the point they are meant to illustrate is not disclosed. In fig. 8, meant to illustrate the end-result of recto-sigmoidectomy for Hirschsprung's disease, the prostate seems to have disappeared and in its place is a structure with a large head and a thread-like tail, suggesting an enormous spermatozoon.

The idea that a group of artists, however good, can teach surgeons their job does not work out in practice.

The Eye in General Practice. By C. R. S. Jackson, B.M., B.Ch., D.O.M.S., F.R.C.S.Ed. Edinburgh: Livingstone Ltd., 1957. Pp. vii and 152. Figures 25. Price 21*s*.

This book represents a praiseworthy attempt to cater for the ophthalmic needs of the general practitioner; there is room for such a publication. Most of the material is acceptable; some adverse comments, however, must be made. There are many useful objects intermediate in size between a hand and a hat-pin for rough testing of the field of vision; few would agree that the most important single measure in the treatment of conjunctivitis is the negative one of avoiding covering the eye. Probing of the naso-lacrimal duct of an infant does not justify the use of a general anæsthetic in skilled hands. Senile cataract does not account for the 'bulk' (if that means majority) of cases on the Blind Register; the figure is about 25%; further, these patients often complain of much more, and more distressing symptoms, than visual loss (p. 63).

There are two serious criticisms of the treatment advised. The treatment of choice for rodent ulcer of the lids is surgery, every time, and not radiotherapy; advice for the use of the latter is copied from book to book and is most unfortunate. Miotics are useless in the treatment of buphthalmos (p. 98) and it is dangerous to say the opposite, for the general practitioner on following this advice might delay referring the case for surgery, the results of which are by no means 'notoriously unsatisfactory'. The book suffers from a defect common to its kind: that of not making clear whether the treatment prescribed is to be carried out by the general practitioner or the specialist. Many forms of treatment advised are outside the scope of the general practitioner.

The Mentally Retarded Patient. By Harold Michal-Smith, Ph.D. Philadelphia: J. B. Lippincott Co.; London: Pitman Medical Publishing Co. Ltd., 1956. Pp. xi and 203. Price 32*s*.

This book is 'written by a psychologist for physicians to equip them to help their retarded patients, and the community and families in which these people live whom society is organized to do without'. The author emphasizes the distinction between intellect and personality, and between mental and manual dexterity. He notices the more advanced legal statutes dealing with mental deficiency in England. This is an affliction which 'handicaps more people than polio or cancer, or even heart disease', but the mentally retarded are not as dangerous to a community as that community can be to them by its bigoted ignorance and cruel indifference. Dr. Michal-Smith sets about his task with sincerity and in good clear English. His two best chapters are on family adjustment and vocational prognosis, but all have the stamp of original thinking; after all, his clinic was, in 1950, the first of its kind in the United States.

The Practice of Psychosomatic Medicine as Illustrated in Allergy. By Hyman Miller, M.D., and Dorothy W. Baruch, Ph.D. New York and London: McGraw Hill Book Co. Inc., 1956. Pp. xi and 196. Price 37*s*. 6*d*.

This book attempts not unsuccessfully to give some understanding of the emotional stresses which may play an important part in the precipitation and maintenance of asthma, eczema and rhinorrhœa. It is mainly concerned with children.

The authors state their views clearly and provide evidence for these in the form of case-histories with actual conversations. Their approach to the asthmatic child and his parents is admirable in its tact and directness. It is difficult, however, not to believe that they have overstated their case: they find, for example, that 97 out of 100 'allergic' children live in an atmosphere of maternal rejection which in every case preceded the onset of symptoms. Modern psychiatric opinion is that a much wider variety of emotional stress may be responsible for triggering these symptoms. Who, for instance, does not recognize the asthmatic only child 'smothered' in genuine but misguided love? One also gains the impression that therapy of a very

superficial nature is all that is required to achieve recovery, but this may be due to the concentrated form of the book whose subject matter is limited to 182 pages. Although the authors accept the importance of allergic sensitivities in asthma, it is not clear what they consider to be the relationship between emotion and allergy.

In spite of these objections there is much in the book which may help the doctor who is interested in asthma to understand the importance of emotional factors in this condition.

NEW EDITIONS

Textbook of Medicine, edited by Sir John Conybeare, K.B.E., *M.C.*, D.M., F.R.C.P., and W. N. Mann, M.D., F.R.C.P., in its twelfth edition (E. & S. Livingstone Ltd., 42*s*.) has been thoroughly revised and brought up to date. Dr. Denis Brinton has completely rewritten the section on diseases of the nervous system, and Professor R. E. Lane has cooperated in the revision of the section on lead poisoning and other industrial diseases. New contributors include Dr. Wilfrid Oakley, who writes the section on diabetes mellitus, and Dr. George Wells, who is now joint-author, with Dr. Dowling, of the section on diseases of the skin. This new edition well maintains the traditions of a book which has for long established itself as one of the best textbooks of medicine for the senior student.

Symptoms and Signs in Clinical Medicine, by E. Noble Chamberlain, M.D., M.SC., F.R.C.P., in its sixth edition (John Wright & Sons Ltd., 35*s*.) remains one of the best books written for the student, bridging the gap between practical and clinical medicine. The text is clear, concise, well illustrated and readable. The student who uses this book in conjunction with his introductory lectures in medicine should start his ward work with the confidence derived from a knowledge of how to tackle a clinical problem. He will continue to find it of value throughout his clinical training and will probably refer to it many years after he has qualified. In a work of this nature, there are bound to be omissions. There is, for instance, no mention of hepatic coma, nor in the paragraph on retinal changes in leukæmia is the appearance of leukæmic infiltration mentioned. Pulsation of the liver is stated to be more easily seen than felt; its association with tricuspid valve disease is not mentioned. These are small criticisms and this book goes far in giving the student the right approach to history-taking and examination.

Clues in the Diagnosis and Treatment of Heart Disease, by Paul D. White, M.D., in its second edition (Charles C Thomas; Blackwell Scientific Publications, 40*s*.) has been revised with meticulous care so as to leave no trace of ambiguity in the interpretation of clues. The reviewer estimates that at least thirty new clues, and five new illustrations, have been added. No clues in the first edition have required deletion in the second. Here is a wealth of sound instruction from a patriarch of cardiology who has culled the world over for all that is best. The new concluding paragraph is a fitting reflection: the need for consideration of the individuality of the patient fully as much as the disease itself, both in diagnosis and treatment.

Recent Advances in Anæsthesia and Analgesia in its eighth edition (J. & A. Churchill Ltd., 40*s*.) is the work of C. Langton Hewer, M.B., B.S., M.R.C.P., F.F.A. R.C.S., and J. Alfred Lee, M.R.C.S., L.R.C.P., F.F.A. R.C.S. It is practically a hundred pages smaller than its predecessor, mainly as a result of the scope of the book having been considerably modified. It now concentrates upon 'recent advances', and as a succinct review of these it will prove of value to all anæsthetists. Among the new sections, reference may be made to those on the phenothiazine derivatives, induced hypothermia, and anæsthesia for cardiac surgery.

Synopsis of Pathology, by W. A. D. Anderson, M.D., F.A.C.P., F.C.A.P., fourth edition (Henry Kimpton, 63*s*.).—Changes and additions to include recent knowledge have been made in every chapter of this well-known volume. Some new illustrations have been introduced and there is a slight increase in size. Although this book is called a synopsis of pathology and the subject is presented in a compact and condensed form, it is very readable and more like a textbook. It remains one of the most useful books of reference for both the pathologist and the clinician.

Aids to Dermatology, by R. M. B. MacKenna, M.D., F.R.C.P., and E. Lipman Cohen, M.B., fifth edition (Baillière, Tindall & Cox Ltd., 10*s*. 6*d*.).—A new edition of this excellent little book should be particularly useful to students and practitioners. It contains almost as much as many textbooks. The subject matter is well balanced, stress being laid upon the most important conditions. It is unfortunate that the use of sulphonamide ointment is still advocated especially in lupus erythematosus, despite the fact that its dangers as a photosensitizer are mentioned elsewhere in the book.

The contents of the July issue, which will contain a symposium on Medical Etiquette will be found on page A104 at the end of the advertisement section.

Notes and Preparations see page 763.
Fifty Years Ago see page 767.
Motoring Notes see page A79.
Travel Notes see page A83.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'CORTIBIOTIC' skin ointment contains soframycin, 1.5%, and prednisolone, 0.5%. It is intended for the treatment of 'eczematous and/or infected skin conditions'. Available in tubes containing 5 g. and 15 g. (Roussel Laboratories, 847 Harrow Road, London, N.W.10.)

'D.F.118' brand dihydrocodeine bitartrate is an analgesic 'comparable with morphine for satisfactory relief of postoperative pain, but strikingly free from side-effects'. Issued in 1-ml. ampoules containing 50 mg., in boxes of 12 and 100. (Duncan, Flockhart & Co. Ltd., 16 Wheatfield Road, Edinburgh 11.)

'FRENQUEL' brand azacyclonol hydrochloride 'has a selective action directed against psychotic states characterized by hallucinations, delusions and confusion'. It is said to be 'extremely safe', and may be prescribed 'without fear of addiction, tolerance, toxicity or side-actions, even in doses considerably above the therapeutic dose'. Successful results are reported in alcoholic hallucinations, postoperative confusion and schizophrenic reactions, and also in combination with chlorpromazine, reserpine and electroconvulsive therapy. Available as 20-mg. tablets in bottles of 100 and 500, and in 20-ml. ampoules containing 5 mg. for intravenous injection, in boxes of six. (Riker Laboratories Ltd., Loughborough, Leicestershire.)

'SULMEZIL V' tablets each contain the equivalent of 60 mg. of penicillin V (phenoxymethylpenicillin) equal to 100,000 units of penicillin G, and 0.5 g. of sulphadimidine B.P. Issued in containers of 25, 100 and 500 scored tablets. (Imperial Chemical Industries Ltd., Pharmaceuticals Division, Fulshaw Hall, Wilmslow, Cheshire.)

'TENSILON' is edrophonium chloride, 'a cholinergic compound which is chemically described as (3-hydroxyphenyl) dimethyl ammonium chloride'. It can be used as a test for myasthenia gravis; 'to differentiate between underdosage and overdosage of a cholinergic drug in a patient with myasthenia gravis'; as an antidote to true curariform drugs, and in the treatment of paroxysmal auricular tachycardia. Available in 1-ml. ampoules containing 10 mg., in boxes of six. (Roche Products Ltd., 15 Manchester Square, London, W.1.)

PHARMACEUTICAL NOTES

BURROUGHS WELLCOME & Co. announce that their preparation 'vasylox' for the relief of nasal congestion is now available in a plastic container designed to deliver drops or spray, as well as in bottles with dropper. (183-193 Euston Road, London, N.W.1.)

ROUSSEL LABORATORIES LTD. announce the introduction of 'precortisyl injectable', each ml. of which contains 25 mg. of prednisolone. Available in 1-ml. and 5-ml. 'multidose vials'. Their hydrocortisone preparation 'hydrocortisyl eye ointment' is now available in an additional strength (0.5%). (847 Harrow Road, London, N.W.10.)

FILM NEWS

Blood is Life (16 mm., commentary; running time 17 minutes) 'tells the story of the organization of the National Blood Transfusion Service and of the meticulous care taken to safeguard donors and patients alike'. The film has been made for the Ministry of Health by the Central Office of Information, and is available on hire (10s. for the first day and a reduced rate for additional days) from the Central Film Library, Government Building, Bromyard Avenue, Acton, London, W.3.

Scientific Film Review for April 1957 contains an interim list of medical films, 1954-56. The total number of medical and allied films reported to the Association to date is 1,611. (Scientific Film Association, 164 Shaftesbury Avenue, London, W.C.2.)

PROBLEMS OF AGEING

NOT less than five awards, of an average value of £300 each, will be made in 1958 for papers descriptive of work in the field of experimental research into problems of ageing. Entries must be received not later than January 1, 1958. Full details can be obtained from Dr. G. E. W. Wolstenholme, Director, the Ciba Foundation, 41 Portland Place, London, W.1.

THE WELLCOME TRUST

THE Wellcome Trust is unique among the charitable bodies assisting scientific research in that its income is derived from a large pharmaceutical undertaking (the Wellcome Founda-

tion Limited), in which the trustees hold all the share capital. Its two functions, as laid down by Sir Henry Wellcome, are the advancement of medical research and the establishment of medical research museums and libraries.

How well the trustees have carried out their onerous duties is admirably brought out in the first report of the Trust, which covers the first twenty years of its activities—from 1937 to 1956. During this period the total benefactions of the Trust have amounted to £1,170,164. The two outstanding items have been the allocation of £135,000 to the Royal College of Surgeons of England for the building and equipment of three new research museums, and the grant of £125,000 to the Royal Society of Medicine to cover the cost of the new Wellcome Research Library. The Trust has also endowed two University chairs in this country, one in Montreal and one in Philadelphia. These are but a few of the many benefactions of a Trust which bids fair to play a role of ever-increasing importance in the development of medical research at home and abroad.

THE CIBA FOUNDATION

CONTINUING its aim of 'promoting international cooperation in medical and chemical research', during 1956 the Foundation provided accommodation for nearly 900 scientists from thirty-one different countries, held five international conferences, six sessions of scientific films and four meetings for the discussion of clinical problems. Under the joint scheme sponsored by the Foundation and the Institut National d'Hygiène, seven British medical graduates visited France and six French graduates visited Great Britain, and the Louis Rapkine Association, designed 'to maintain links between graduates in England and France who have had experience of these and similar scholarships', was inaugurated. These and other activities during the year are outlined in the Foundation's recently published report for 1956.

DR. MERVYN ARCHDALL

THE news of Dr. Mervyn Archdall's retirement from the editorship of the *Medical Journal of Australia* will be received with regret by the many readers in all parts of the world who have appreciated his discriminating editorial pen. For over a quarter of a century he has played an important part in shaping the destinies of the profession in Australia. His outlook has never been parochial, and his writings, often trenchant and sometimes pungent, have done much to ensure that high standard of professional conduct which characterizes Australian medicine today.

TUBERCULOUS STUDENTS

THE British Student Tuberculosis Foundation has issued a brochure describing the facilities which it now offers. These consist of three special units where students with tuberculosis may continue their studies while receiving treatment for, and convalescing from, their illness. One, for men, is at Pinewood Hospital, near Wokingham; one, for women, is at High Wood Hospital, Brentwood, and there is one at Tor-na-dee Sanatorium, near Aberdeen, for Scottish students of both sexes. Further details of the units at Pinewood and Brentwood can be obtained from the Secretary/Administrator of the Foundation, 59 Gloucester Place, Portman Square, London, W.1. Details of the Tor-na-dee unit can also be obtained from here, or from the Scottish Secretary, University Union, Broad Street, Aberdeen.

GENERAL PRACTITIONER LISTS

THE number of general practitioners under contract to provide unrestricted general medical services under the National Health Service in England and Wales on July 1, 1956, was 19,082. According to the Minister of Health, on this date the number of practitioners with lists of between 2,500 and 3,500 patients was 5,385; the number with lists of between 1,500 and 2,500 was 5,218; and the number with lists of 1,500 or under was 5,500, of whom about 540 had lists of 500 or under.

1956 MORTALITY

DEATHS from tuberculosis continued to fall, whilst those from cancer continued to rise in 1956, according to the provisional figures for England and Wales issued by the Registrar General. The total number of deaths from respiratory tuberculosis was 4,851, compared with 5,837 in 1955; this gives a death rate of 109 per million persons, which represents a fall of more than 75% since 1947. The death rate from all forms of cancer was 2,274 per million for men and 1,891 for women; the 1955 figures were 2,252 and 1,873 respectively. Of the 48,932 male deaths from cancer, 15,615 (32%) were due to cancer of the lung and bronchus, whereas only 2,570 (6%) of the 43,769 female deaths from cancer were due to this cause.

The maternal mortality rate (including abortion) in 1956 was the lowest ever recorded: 0.56 per 1000 live and stillbirths.

THE PROFESSIONAL FATE OF MEDICAL STUDENTS

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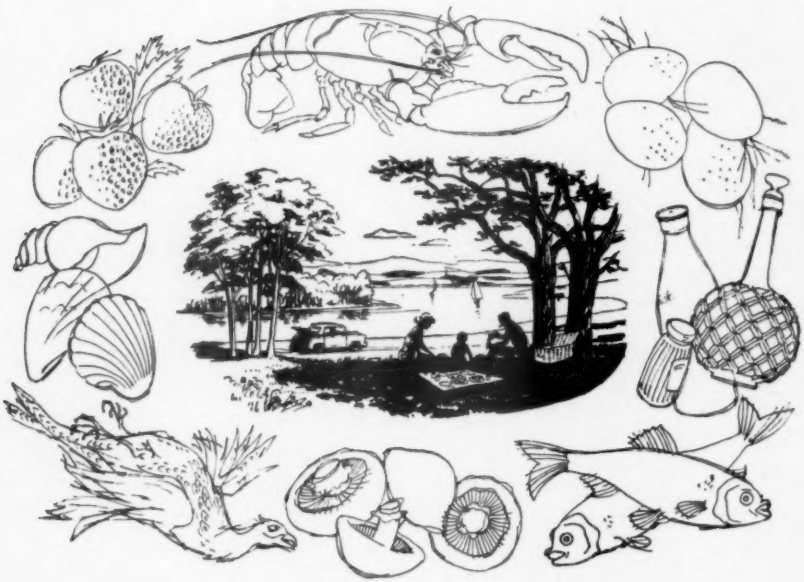

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of the 1,052 (87%) from whom information was obtainable, only 471 are engaged in 'general practice type of work', whereas 429 are doing 'specialist work' including 300 consultants. In other words, less than 50% of all graduates from St. Thomas's were engaged in general practice. The remaining nine categories include 'other activities—medical journalism, coroner, etc.' (12), and 'no medical work' (10). Remarking on these figures in the April issue of *St. Thomas's Hospital Gazette*, the Secretary of the Medical School, Dr. A. L. Crockford, writes: 'These tables should be seriously considered when changes in the curriculum of the medical student are being considered'.

PÆDIATRICS IN MEDICAL EDUCATION

As 'at least one-third' of the working time of general physicians is spent in the care of children, 'medical education everywhere should include serious and complete training in pædiatrics' is the recommendation of the World Health Organization study group on pædiatrics. Their report states that it is impossible to do justice to the pædiatric curriculum in less than 300 hours of teaching and practice and emphasizes that 'normal growth and development, as well as preventive and social aspects, should be stressed in pædiatric teaching in all countries of the world'.

MENTAL HEALTH IN THE UNITED STATES

AT a recent meeting of the American Public Health Association it was reported that about 10% of all people living in big cities in the United States are mentally ill. This was considered to be a conservative estimate.

DOGGER BANK ITCH

CONTACT dermatitis due to the 'sea chervil' (*Alcyonidium hirsutum*), or Dogger Bank Itch as it is commonly known, is one of the recognized occupational hazards of fishermen in the North Sea. It has been recognized in the Danish Workmen's Compensation Act since 1939. In reporting a case of twenty years' standing in the skipper of a trawler, R. H. Seville (*Brit. J. Derm.*, 1957, **69**, 92) notes that in this country cases are seen mainly at Grimsby and Lowestoft where the fish from the Dogger area is landed. Seville's patient first developed the condition in November 1934 when fishing off the North Dogger. His arms became swollen to one and a half times their normal size: this is said to be a feature of the illness recognized by the fishermen themselves. The degree of sensitivity that can be achieved is illustrated by the fact that even going on to the fish wharves at Grimsby makes his face burn and tingle, and has on occasion started an attack. Danish dermatologists warn against attempting desensitization of those who are very sensitive, as severe reactions may be induced with the smallest dose of allergen.

SELF-TREATMENT BY ANIMALS

THAT animal self-treatment may extend to the ingestion of certain plants as antidotes for poisoning is 'a strong possibility' is the opinion of L. H. Roddis in a recent article in *Current Medical Digest*. 'In India the ichneumon, or mongoose, is a killer of snakes and does not hesitate to attack even the deadly cobra. When bitten they seek and eat the leaves of the ophiorhiza and this has led the natives to use the leaves and juices of the plant as a dressing on snake bites'.

Two reasons are given why dogs, foxes and other carnivora eat grass. The long coarse blades are eaten to excite vomiting, whilst small tender vegetation is eaten 'in the instinctive search for food that contains antiscorbutic properties, or for trace elements needed'.

PUBLICATIONS

Advice to the Expectant Mother, by F. J. Browne, M.D., D.SC., F.R.C.S.ED., F.R.C.O.G., and J. C. McClure Browne, B.SC., M.B., B.S., F.R.C.S.ED., F.R.C.O.G., eleventh edition, covers adequately and simply what an expectant mother, without any special training, ought to know about pregnancy and labour, the benefits of antenatal care, and breast feeding and care of the baby. The advice is sound and the book can be thoroughly recommended to the readers for whom it is intended. (E. & S. Livingstone Ltd., price 15.)

Dorland's Illustrated Medical Dictionary, in its twenty-third edition (W. B. Saunders Co., 87s. 6d.), has lost its original editor, Dr. W. A. Newman Dorland, who died last September at the ripe old age of 92. His world-famous dictionary, however, which now bears his name, will long remain as a fitting memorial to an outstanding member of the profession. The new edition has been thoroughly revised, with various additions and emendations, which add considerably to its practical value. Like preceding editions, it is characterized by its thoroughness, accuracy and skill of definition. It is indeed one of the notable books of reference in the world of medicine.

Lecture notes on the use of the microscope, by R. Barer, *M.C.*, M.B., B.S., second edition (Black-

well Scientific Publications, 7*s.* 6*d.*).—The first 27 pages are given to a plain explanation of the structure and theory of the microscope. The next 30 pages describe simply and thoroughly the technique of using the instrument. Both are excellent. A copy should be issued chained to every microscope. It can be recommended without reserve to all microscopists.

Chronic Bronchitis—An NAPT Symposium contains authoritative and stimulating accounts of a neglected disease, presented by a bacteriologist, pathologist, radiologist, clinicians and others. The many comments on current thought and study are particularly interesting but disappointingly brief. Although the symposium also suffers from the absence of editorial control it should nevertheless be profitable reading, particularly for general practitioners and physicians. (National Association for the Prevention of Tuberculosis, price 6*s.*)

Medical Officers of Health 1848 *to* 1855, by Professor Fraser Brockington, M.D., D.P.H., is a reprint of two articles originally published in *The Medical Officer*. They cover a hitherto neglected decade in the history of public health, and will be read with interest by all who are interested in this critical period in the development of the public health services of the country. (Hodgetts Ltd., Chronicle House, 72/78 Fleet Street, London, E.C.4, price 10*s.*)

Education of the Public Regarding Cancer is the report of the conference on this subject held in January. It consists of three papers: 'The prevention and treatment of cancer' by Mr. R. W. Raven; 'Problems of cancer education' by Dr. John Burton; and 'Cancer education in practice' by Dr. John Wakefield. (The Central Council for Health Education, price 1*s.*)

Your Blood Pressure and How to Live With It, by William A. Brams, M.D.—If you believe your patients can benefit by knowing the right things about their own bodies and minds, this is one of the books you will recommend. It should help patients with 'blood pressure' in this country, as well as those in America for whom it was written; it should also interest their families, and even their medical attendants. Dr. Brams has already shown that he can put across his ideas for lay readers. In this book many familiar notions, particularly about diet, exercise and rest, are brought into sharp focus. Running through all the chapters is a vein of encouragement and optimism. (Staples Press Ltd., price 15*s.*)

Il Kwashiorkor, by A. Bendandi and C. Bellucco, is a review of the literature on the very topical subject of kwashiorkor and the subject-matter is based not only on the authors' reading but on correspondence they have had with many of the foremost workers in this field. The condition is dealt with under the usual headings including nomenclature and history, geography, pathology, diagnosis and treatment, and its relationship with other tropical liver diseases is discussed. No less than 937 references are cited up to September, 1955. This work is a labour of love for which the Italian-reading doctor will be grateful. It would be useful if it were available in the English language. (*Omnia Medica*, price L.2000.)

National Register of Medical Auxiliaries.—The Registers of Dispensing Opticians, Orthoptists and Operating Technicians for 1957 have just been published. Copies will be supplied free to members of the medical profession on application to the Registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London, W.C.1.

B.C.G. Vaccination against Tuberculosis is a series of questions and answers designed 'to explain the facts about B.C.G. vaccination'. (Research Defence Society, price 3*d.*)

Four addresses on cerebral palsy given at a conference for members of the medical profession in Birmingham in 1956 are published in a booklet issued by the British Council for the Welfare of Spastics, price 3*s.* 6*d.*

Administration of Maternal and Child Health Services, W.H.O. Technical Report Series No. 115, is the second report of the expert committee on maternal and child health. Principles of programme planning, organization and structure of maternal and child welfare services, and techniques of administration are fully examined. (H.M. Stationery Office, price 1*s.* 9*d.*)

Corrigendum.—Dr. I. A. B. Cathie writes: In my article in the February issue (p. 174, line 28), the dosage of ferrous gluconate for infants should read '20 mg. three times a day at birth, rising to 50 mg. at one year'.

INDEX AND BINDING CASES

The index to Vol. 178 (January-June 1957) will be forwarded to all subscribers with the July issue. Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 5*s.* 6*d.* each, post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 13*s.* 6*d.* per volume; this includes the cost of binding case and return postage.

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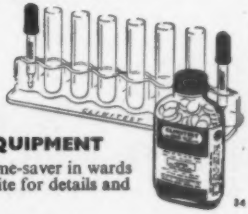

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THE PRACTITIONER
Fifty Years Ago

'Who satisfieth thy mouth with good things; so that thy youth is renewed like the eagle's'.—
Psalms CIII, 5.

JUNE, 1907

FIVE-AND-A-HALF out of the seven pages of 'Notes by the Way' this month are devoted to 'Food Fads': 'The diet reformer is abroad in these days, and every month witnesses the birth of a new food fad. We have the Fletcherites, who, so far from not giving two bites to a cherry, insist on thirty-two to a mashed potato, and who even profess to chew their milk . . .; the followers of Chittenden, who weigh their food and count the morsels, and would seem, like Sanctorius, to pass the greater part of their lives in a balance; the devotees of Dewey, who teaches that the secret of a healthy life is to eat no breakfast; the followers of Salisbury with their raw minced beef and hot water . . .; Mr. Bernard Shaw with his "grape nuts"; Mr. Eustace Miles, with his "rissoles with curry flavour", his "rice cutlets", and his "vegetable roast"; Dr. Haddon with his apples. . . . Then there is Professor Metchnikoff, who says that if we wish to rival the patriarchs in longevity we must kill all the "wild" microbes in our intestinal tract by drinking his special elixir, Bulgarian sour milk; some who have tasted it have said that they would prefer a short life to length of days saddened by frequent draughts of the genuine *Kisselo Meklo*'.

The first of the 'Original Contributions' is by Raymond Crawfurd, M.D., F.R.C.P., Physician to King's College and the Royal Free Hospital, who deals with 'Tricuspid Regurgitation'. 'Duodenal ulcer', writes B. G. A. Moynihan, M.S., F.R.C.S., 'has been considered an extremely rare disease. It was said by Obermayer that its diagnosis is "frequently impossible, or can be made only with more or less probability", and, again, that "the prognosis, provided that the diagnosis can be made at all, is always very serious". . . . I hope to show that the duodenal ulcer is common, that its diagnosis in the great majority of cases is quite easy, and that its surgical treatment is the safest, indeed, often the only reasonably safe treatment, that can be adopted. . . . The fact that one surgeon has operated upon 114 cases disposes of the statement that duodenal ulcer is rare; on the contrary, it is frequent. Its supposed rarity was due to an inability on our part to make an accurate diagnosis; the living pathology had not been studied to a degree permitting us to make the diagnosis with such certainty as is now possible'.

In an article with the arresting title 'The Pretuberculous Stage of Pulmonary Tuberculosis', J. J. Galbraith, M.D., Medical Superintendent, Ochil Hills Sanatorium, Kinross-

Sir William Jenner, Bt., G.C.B., M.D.
(1815-1898)

shire, writes: 'The early physical signs of pulmonary tuberculosis do not correspond with the commencement of the disease. For a prolonged period, previous to diagnosis, the disease is advancing from a small deep-seated lesion and causing a toxæmic condition setting up various symptoms, and modifying the course of intercurrent diseases. The variety and continuance of these symptoms constitute a clinical picture, which, when recognized by experience, should suggest the possibility of latent tuberculosis. . . . In cases, in which a tentative diagnosis is followed by appropriate treatment, the results justify the course adopted'. In the

writer's opinion estimation of the opsonic index as a means of diagnosis 'promises to prove of great value'.

Leonard Rogers, M.D., F.R.C.P., F.R.C.S., Professor of Pathology, Medical College, Calcutta, discusses 'The Early Diagnosis and Cure of the Presuppurative Stage of Amœbic Hepatitis': 'Personally, I look on ipecacuanha as invaluable in the treatment of amœbic dysentery, in fact as a specific against that disease, and in Lower Bengal, where amœbic liver abscess is so common, I regard this drug as second only in importance to quinine itself. If this is so, it is easy to understand how large doses of ipecacuanha . . . may rapidly abort an early presuppurative amœbic hepatitis by curing the latent amœbic dysentery that produces it'.

C. O. Hawthorne, M.D., M.R.C.P., Physician to the Central London Ophthalmic Hospital, reports two cases of retinal embolism in which a normal standard of central visual acuity was retained. C. F. Hadfield, M.D., of Malvern, writing on 'The Treatment of Dropsy by Deprivation of Salt', refers to the successful treatment by Widal and Javal of patients with parenchymatous nephritis by reduction of the amount of salt in the diet. Some of the results which he enumerates 'are so striking that it is curious that they have received so little attention in this country. Some time ago, at the suggestion of Dr. Herringham, I made prolonged observations on three cases of ascites, and one case of parenchymatous nephritis, which were treated alternately on saltless and salt-containing diet. . . . In all cases we found that deprivation of salt seemed to exercise a beneficial effect, not so much in dispersing the fluid, as in delaying its accumulation. Even though in our hands the treatment proved far less successful than in France, still the slight advantage we found was quite sufficient to justify its use'.

A new series of articles entitled 'Modern Leaders in Medicine' begins in this issue with Sir William Jenner, 'for many years the acknowledged head of the medical profession of this country, and the foremost member of the staff of University College Hospital at the time of its greatest renown. For several years he ruled the London College of Physicians with a strong hand. He was for a long time the trusted counsellor of a Sovereign, whom long experience had made an unusually good judge of men, and she had the insight to detect the sterling worth of the man beneath the blunt manner . . . unlike many of the Olympians of Medicine, he would take a suggestion from a clinical clerk or even a nurse, if he thought it sound. . . . The extent to which Jenner's teaching infiltrated the minds of the men, who came under its influence, can be adequately estimated only by those who know what the art of healing was in his early days'. W. R. B.

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MOTORING NOTES

Touring in Italy

By ROBERT NEIL

AT the end of a previous article in *The Practitioner* I promised to elaborate on the subject of foreign touring by describing time-saving routes to Italy. It may seem wrong to give any attention to the saving of time when on holiday, as that is certainly when one should relax and let time pass by in an attempt to forget the tyrannical timetable of everyday life. As the time most of us can devote to annual leave is limited, however, it is often worth while trying to reduce the time spent on the outward and homeward trips, to allow more time to be passed at the selected holiday centre.

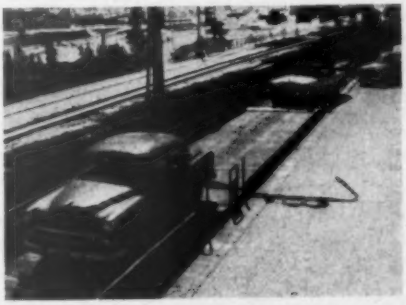
Many every-day motorists avoid the obviously shortest route to Italy—by way of Switzerland and over the Alps—through fear of the high mountain passes, but this problem is very easily solved by using either the Simplon or the St. Gotthard tunnel. As an indication of the time that can be saved on this route many British competition motorists habitually do the journey between London and Milan within twenty-four hours. Admittedly not many motorists would wish to emulate this performance, but it could not be equalled by the hardest driver if he went by way of either the Mont Cenis or the Ventimiglia frontier posts. I find it difficult to understand those motorists who, intending to spend their holiday in either Italy or Spain, are prepared to employ one-third of their total holiday time motoring there and back. If advantage is taken of the week-ends at both ends of one's annual three weeks' holiday it seems to me much better to accept, say, four days for hard driving, so that as long as possible can be spent at one's destination. I agree that it is better to travel hopefully than to arrive, but there are few of us with time to motor that way always.

THE STARTING POINT

It matters little which French port is the starting point for one's journey to Italy, as the routes converge conveniently, although it is perhaps simplest to start from Dunkirk or Calais. The route I suggest is by way of Arras, Laon and Rheims to Vitry-le-François and Chaumont. From here N19 is followed to Vesoul and Belfort to Basle. The route through Switzerland which I recommend is that by Lucerne and Schwyz, which leads to the St. Gotthard and the frontier. The loading point for cars intended for passage through the tunnel is Goschenen, the unloading point being at Airolo, which despite its Italian-sounding name is still in the Confederation. Loading and unloading are simplicity itself, as it is only necessary to drive straight on to flat cars from a loading ramp. The journey through the tunnel of the St. Gotthard takes only twenty minutes, and it would be a good driver who would manage the crossing of the pass in less than one hour. At both Goschenen and Airolo there are excellent restaurants in the stations, so the short time waiting for the next train can be well spent. An alternative, but slower, route is to continue south from Langres to Besançon and Lausanne, from where the road through Montreux can be followed along the valley of the Rhône by way of Sierre to Brig, where the tunnel through the Simplon can be used to Domodossola.

INTO ITALY

For motorists anxious to see a little more of the Alpine scenery, and prepared to sacrifice some time to do so, there is a most pleasant deviation



Cars being driven on to the special flat rail-cars for the journey through the St. Gotthard Tunnel in Switzerland.

to be taken north of Goschenen. If this is done I would suggest staying the night in Amsteg where there is a very pleasant hotel, only a few miles north of Wassen, and making an early start the following morning. At Wassen the turn to the west should be taken to Innertkirchen over the wonderful Susten Pass, and then the Grimsel and Furka Passes can be followed to the Rhône Glacier. After lunch one's steps can be retraced slightly and the road taken to Brig, and either the Simplon Pass or the tunnel can be used. If Italy is entered by Domodossola one will go naturally by the southern end of Lake Maggiore, but if entering by the St. Gotthard route there are alternative ways from Bellinzona onward. One can go straight by way of Lugano and Como, or turn slightly westward and take the road down the length of Lake Maggiore.

'The latter is my own favourite, but largely because of a specially attractive hotel at Cannero. This village has the unusual advantage for a lakeside Italian village in being by-passed by the main road. This means that meals and rest are not disturbed constantly by hordes of long-distance coaches with their strident horns, and innumerable scooters.

THE ITALIAN LAKES

Having discussed short cuts to Italy it is only fair to consider the desires of motorists who have become a little tired of the much publicized beauty spots on the Italian Riviera. For those many visitors from Britain, who perhaps find the excessive heat too much for them in many parts of Italy, I would suggest considering the lake district, and the Lake Maggiore area in particular. Cannero I have already mentioned. From here it is possible to make many interesting day excursions into the hills on either side of the Lake, as there is a constant ferry service between Pallanza and Làveno, which allows one to penetrate in to the hills above Luino skirting the Swiss frontier. In the hills behind Stresa, where world peace was 'assured' so many years ago, are both Lago d'Orta, with one of the many lovely sanctuaries dedicated to St. Francis, and Macugnaga on the shoulders of Monte Rosa.

HOME BY PARIS

If one has womenfolk in the car it will be almost impossible to avoid at least pausing in Paris, but for financial reasons I recommend that this should be done on the way home, when it is easier to gauge how stupidly generous one can be. Bearing this in mind a good there-and-back route would be to go to Italy by Basle and the St. Gotthard, and return by the Simplon and Lausanne. On regaining the common route at Langres only the few miles to Chaumont will need to be covered before branching off for Paris by way of Troyes. A quick glance at the Michelin Guide, or Hallwag, will prove what a saving in time and mileage the routes I have described offer, as compared with going farther south in France.

STUDYING SPECIFICATIONS

In a letter I received recently a reader asked what exactly it was possible to deduce from a study of the specification details of different cars. A complete reply to this query could fill many pages of *The Practitioner*, as it would be necessary to describe in detail the design of many different cars. It must first be appreciated that the design of any flow-production car must be a compromise, in an effort to satisfy the requirements of as many potential purchasers as possible. For example, many motorists want a car which will do almost all its work in top gear, and will require the minimum of gear changing, even when being driven in heavy traffic. To satisfy such motorists the design staff will feel tempted to provide a three-speed gearbox, but this can produce the disadvantage that an individual driver who habitually employs a high cruising speed will find that the engine is being overstrained. The motorist who wants a high cruising speed will often find it better to have a four-speed gearbox, but this will almost certainly mean that a change down through third gear to second will be required when driving in city traffic. Even the over-all dimensions of a car can indicate its likely character. The cost of a flow-production small car, intended for sale at a very low price, is roughly proportional to the amount of metal actually used in its construction. It follows therefore that the shorter and narrower the car, provided four seats can just be fitted in, the cheaper it can be sold, or the greater can be the margin of profit for its builder. Let us assume that there are three hypothetical cars all with equal wheelbase but with wide variations in width of track. The car with the widest track—all other things being equal—will be the most stable.

ENGINE SPEED AND ROAD SPEED

Another technical point on which there is much confusion concerns engine speed in relation to road speed. Many motorists believe that the lower the engine speed the longer will be the life of the engine, but it has to be remembered that the most vital factor in obtaining longevity is the actual speed of the pistons. On an engine with a very long stroke the speed of the pistons up and down the cylinder walls is higher for a given crankshaft speed than on an engine of the same total capacity, but with a bigger bore and a much shorter stroke. A moment's thought will clarify this; obviously the farther the piston has to travel in a given moment the higher must be its speed. As there is a limit to the piston speed which can be reliably used for long periods, it follows that the car with a long stroke engine will have a lower reliable theoretical cruising speed than the short-stroke engine—unless the manufacturer has fitted an artificially high top gear ratio to keep the piston speed down. When studying the specification of two rival makes, therefore, that with a long stroke engine but a high top gear should be regarded with suspicion because, if the power output and weight of the two cars are equal that with the artificially high top gear will have poor acceleration, particularly on top gear and at relatively low road speeds.

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TRAVEL NOTES

Treasures of the North

By PENELOPE TURING

NEWCASTLE, which will be a focal point for many doctors next month, makes an ideal centre for exploring northern England. Given a little time and petrol, the wealth of historic towns and villages and the variety of the country itself are amazing, and quite unexpected to those who know the district only from the stern purposefulness of the Great North Road.

Northumbria has been a highway and a battleground of history for two thousand years. Early Britons and warring Scots, Roman legionaries and mediæval armies marched and fought over it. Early Christians built their churches and abbeys when a lifetime was well spent in raising a monument to faith, and their strength and beauty have endured the centuries. Kings and nobles set up the might of their castles. Legend and history lie like a cloud pattern across its hills and valleys, and the self-torments of an adolescent age fall into perspective in a land which has absorbed the spirit of a hundred generations.

HADRIAN'S WALL

In A.D. 122, the Emperor Hadrian came to Britain and ordered the erection of a defensive wall which should mark the northern boundary of Roman territory. Originally it ran for 73½ miles from Wallsend at the mouth of the Tyne to the Solway Firth at Bowness. Centuries of later builders robbed the Wall of its stone and demolished parts of it for their own developments, but long sections of it, particularly in the centre, still remain. By driving out to Chollerford, 23 miles west of Newcastle, one can explore one of the most famous forts on the Wall, Chesters, and here, too, are the remains of the Roman bridge over the North Tyne. For the energetic walker it is well worth while to follow the Wall westwards from here to the Cumberland border, for much of the wild country to the north must be almost unchanged since the Romans kept watch there against northern raiders. The George Hotel at Chollerford, or the Angel at Corbridge, are good for a meal en route.

Just south of Chollerford is Hexham, with its beautiful Priory church which was founded by St. Wilfrid in the 7th century. It has a Saxon crypt, but the existing building is a blending of old and new, parts go back to the early 13th century whilst the nave was not com-

pleted until 1908. There is a fine 15th century Moot Hall in the town.

THE NORTHUMBRIAN CASTLES

For a longer tour there are the castles along the coast. Follow the Great North Road about 25 miles up to Thirston and then take a small

Part of the Roman Wall near Winshiels Crag

country road to the coast at Amble and Warkworth. Warkworth Castle, a ruin dating from about 1200, stands on a hill almost surrounded by a loop of the river Coquet which enters the sea here. The castle was for centuries one of the seats of the great Percy family, Earls and later Dukes of Northumberland. A little way up the river is a remarkable 14th century chapel hewn out of solid rock, known as the Hermitage, which was originally used by priests under the Percy patronage.

North again by the coast road is Dunstanburgh Castle, standing on a sheer cliff 100 feet above the sea, and beyond this, Bamburgh Castle. To me, Bamburgh is one of the most dramatic-looking castles I have seen. It, too, stands on the cliff edge, a magnificent typical Norman keep surrounded by the later walls of the inner and outer baileys. A good deal of restoration has been done and later buildings added, but it has the real atmosphere of a fortress. Legends link it with the Arthurian saga, for an earlier Bamburgh Castle was one of the places claimed to have been Lancelot du Lake's Joyous Guard.

FLODDEN FIELD

North-west from here is the fascinating village of Ford, and close by Flodden Field, where the battle of 1513 brought crushing defeat to James IV of Scotland but immortality in history. North lies the smiling valley of the Tweed and the Border country, south-west the great mysterious rampart of the Cheviots. To return to Newcastle we take a main road south to Wooler and branch off to Alnwick on the Great North Road again. Alnwick, apart from being famous as a home of fishing tackle, is a pleasant little old-world town with another well-known castle still in the possession of the Duke of Northumberland.

THE LAKE DISTRICT

Away to the west there is of course a different world, better known for its natural beauties than Northumberland—the Lake District. Derwentwater, perhaps the most beautiful of all with Borrowdale and Scafell folding away range on range beyond its head; Grasmere where the great Lakeland sports gathering will be held on August 22; Windermere for sailing and the crowded summer lake steamers; Ullswater where Wordsworth's daffodils bloom in spring. Some books are more real to one than the actualities of every-day life. I wonder how many of us will always see the Lake District through the books of Arthur Ransome, which have already delighted the children of two generations. Certainly they form one of the best introductions to this countryside.

DURHAM AND THE DALES

Southwards comes Durham with its magnificent cathedral and castle towering above the river Wear.

And so to Yorkshire and its dales. Richmond in Swaledale is one of the most fascinating little towns I know, its cobbled streets winding up the hillside from the river to the ruined castle above. I remember exploring this in the winter of 1946/7 when the whole countryside was still

Alnwick Castle and the Barbican

and white, and the only sound the heavy plop-plop of snow being shovelled off the top of the keep.

If you can spend two or three days on this particular tour you can go on to Leyburn, then up Wensleydale (the valley of the Ure) to Hawes. This is the centre for Wensleydale cheese. It

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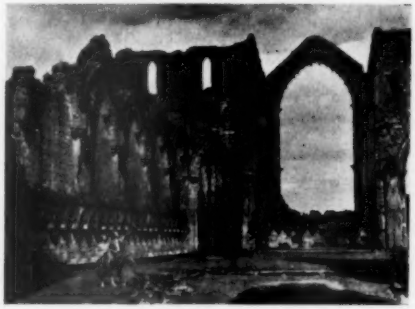
is now made in factories, but is still one of the very best of the English cheeses. Turning south here you cross over into Wharfedale to Kettlewell, then down past the beautiful riverside ruins of Bolton Abbey to Bolton Bridge where you go east to Blubberhouses, Pateley Bridge at the foot of Nidderdale, and Ripon. This is another old-world city with a charming small cathedral where the work of several centuries of mediæval builders is fused into one.

FOUNTAINS ABBEY

By this route you will come first to Fountains Abbey, but for the most striking impression it is better to approach it from the direction of Ripon. Few places in England are as beautiful as Fountains Abbey, its soaring lines standing secure and tranquil among the trees and smooth green grass. Roofless and ruined it may be, but the spirit of past might lingers among the shadows of its walls. This is one of the many places in Yorkshire where the Robin Hood legends crop up, for it was in Fountains Dale that Friar Tuck lived as a hermit until his famous fight with Robin Hood converted him into one of the Merry Men. From Ripon the Great North Road is only about 4 miles to the east.



Fountains Abbey

But these are only a few of the high lights. Northumberland, Durham, Cumberland, Westmorland, Yorkshire all have lovely valleys and staunch little towns and villages, comfortable inns and half-forgotten landmarks of the past. An exercise with a map will decide which to visit and what to leave unseen.

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FURTHER RESEARCH has now been done into the irritant effects of aspirin upon the gastric mucosa. A detailed report on this work appears under the heading "Aspirin and Ulcer" in the B.M.J., July 2, 1955.

The summary of the discussion appended to this report is as follows:

"Aspirin is a serious gastric irritant, particularly in peptic ulcer patients."

Here is a further extract from the report:—"In conclusion it is suggested that aspirin should never be given to patients with peptic ulceration, or indeed to those who have any gastric intolerance to it, however mild. Such an instruction should be given a prominent place in peptic ulcer advice charts, usually in place of much that could be safely left out. Some of these patients took aspirin on a full stomach only in powder form, with serious results, and, although this method almost certainly mitigates its irritant effects, it does not guarantee immunity. Calcium aspirin does not have this irritant action unless it has deteriorated through standing, and it can be used with impunity, especially if prescribed in soluble form. This simple measure would, in our opinion, cut down significantly the incidence of haematemesis and exacerbations of ulcer symptoms."

SOLPRIN provides calcium aspirin in pure and stable form.

CODIS is a compound tablet that provides codeine and phenacetin and calcium aspirin, in place of the ordinary aspirin in Tab. Codein. Co. B.P.

Neither SOLPRIN nor CODIS is advertised to the public.

RECKITT & COLMAN LTD., HULL & LONDON (PHARMACEUTICAL DEPT. HULL)

The Medical Service of the Royal Navy

VACANCIES FOR MEDICAL OFFICERS

Candidates are invited for Short Service Commissions of 3 years, on termination of which a gratuity of £450 (tax free) is payable. Ample opportunity is granted for transfer to Permanent Commissions on completion of one year's total service. Officers so transferred are paid instead a grant of £1,500 (taxable).

All entrants are required to be British subjects whose parents are British subjects, to be medically fit, and to pass an interview.

Full particulars from the Admiralty Medical Department, Queen Anne's Mansions, St. James's Park, London, S.W.1.

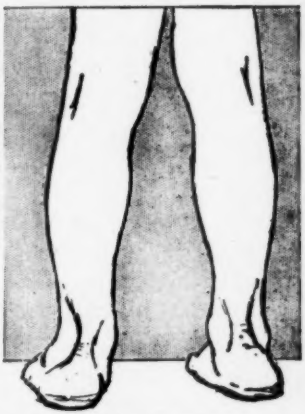
How do *YOU* tackle flat foot?

. . do you prescribe an external wedge on the shoes?

BUT the wedges soon wear away; and very often the child is made to feel self-conscious because his shoes look different from other children's.

Surely it's more logical to have a wedge *built-in* between the inner and outer sole—invisible, and completely unaffected by wear or repair of the shoe. That is how Start-rite INNERAZE shoes are made; why they are the only practical solution to this problem.

Information from Mr. W. J. Peake, James Southall & Co. Ltd., Crome Road, Norwich.



INNERAZE

Invisible Wedge Shoes by START-RITE

(who make the finest children's shoes of all types)

Inneraze Shoes are supplied only against medical prescription

Bacteriologically tested and specially designed for the prevention of droplet infection

The "Cestra" Mask

FOR SURGEONS AND NURSES

After many bacteriological experiments this mask was designed to arrest all droplets from the mouth and nose, and so to prevent contamination during operation. The "Cestra" Mask consists of four layers of fine dental gauze. It fastens securely under the chin, has an air gap at the sides, is comfortable to wear for long periods and may be easily sterilised.

Obtainable from Chemists and Medical Stores

MADE BY ROBINSON & SONS LTD., Wheat Bridge Mills, Chesterfield
Tel. Chesterfield 2105 *London Office:* King's Bourne House, 229/231 High Holborn, London, W.C.1 Tel. Holborn 6383 *Manufacturers of all kinds of Surgical Dressings*

Rubriment relieves pain in such conditions as muscular rheumatism, fibrositis, strains and sprains.

Some minutes after application the skin becomes flushed and there is a comforting feeling of warmth which persists for many hours.

RUBRIMENT

A new long-acting rubefacient—safe and effective

RUBRIMENT contains a new substance, the benzyl ester of nicotinic acid, which gives a long-lasting rubefacient effect. Experimental studies have shown that even after prolonged and repeated application no damage or irritation to the skin structure was caused.

Ten minutes after application there is a feeling of warmth and the area becomes flushed. This redness is due to the dilation of the small cutaneous blood-vessels. Clinical reports have been received of the efficacy of Rubriment for relief in such conditions as muscular rheumatism, lumbago, fibrositis, strains and sprains. The immediate and prolonged vasodilatory action of Rubriment also provides relief for unbroken chilblains.

Available in two forms Rubriment (2.5% nicotinic acid benzyl ester and 0.1% Capsicin) is available either as a cream or as a liniment, both of which are non-greasy.

The cream is rapidly absorbed and needs only gentle application. It is supplied in tubes of 20 g. (approx.). Basic price to N.H.S., 2/2d.

The liniment lends itself to massage, if this is required. It is supplied in bottles of 2 fl. ozs. (approx.). Basic price to N.H.S., 3/-.

Directions for use One application per day has been found to be effective for the majority of patients, though a fresh application may be made, if necessary, at more frequent intervals. *Rubriment is not advertised to the public and can be prescribed on E.C.*10.

RUBRIMENT Horlicks Limited

PHARMACEUTICAL DIVISION SLOUGH BUCKINGHAMSHIRE

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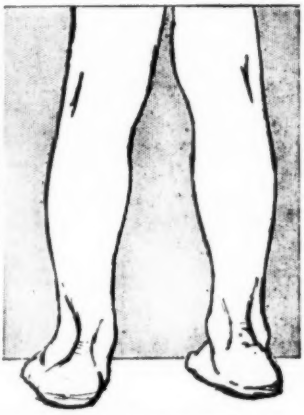

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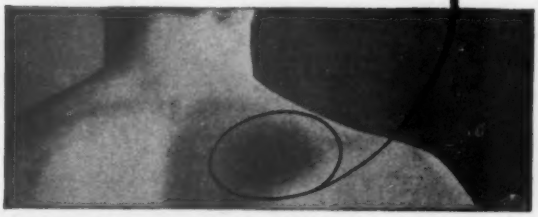

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RUBRIMENT Horlicks Limited

PHARMACEUTICAL DIVISION SLOUGH BUCKINGHAMSHIRE

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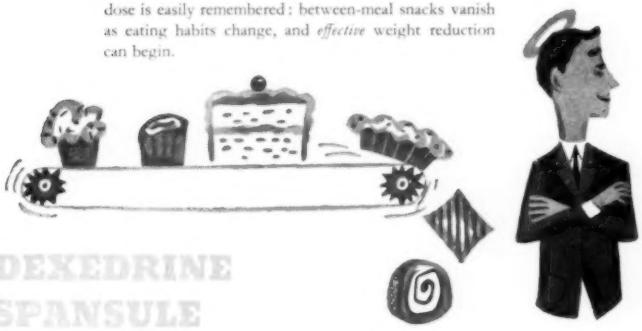
For the between-meal nibbler every toothsome morsel is an irresistible temptation. 'Conveyor belt feeding' becomes a habit that punctuates his day with an endless series of 'little somethings'—most of them starchy and all of them fattening. With each surrender to temptation his girth grows greater and his will to resist is less.

'Dexedrine Spansule' capsules put temptation behind him by controlling his appetite all day long—*between meals as well as at mealtimes.* The single morning oral dose is easily remembered: between-meal snacks vanish as eating habits change, and *effective* weight reduction can begin.



DEXEDRINE SPANSULE

SUSTAINED RELEASE CAPSULES

control appetite in weight reduction

Smith Kline & French Laboratories Ltd., Coldharbour Lane, London SE5

SUDP126 (col)

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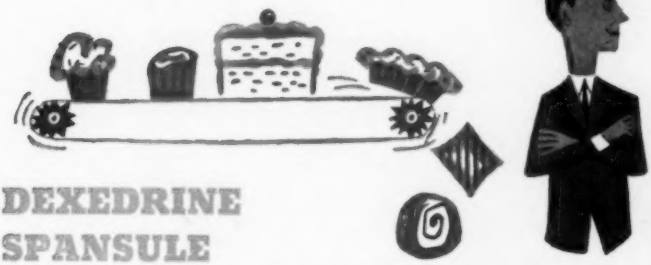

DEXEDRINE SPANSULE

SUSTAINED RELEASE CAPSULES

control appetite in weight reduction

Smith Kline & French Laboratories Ltd., Coldharbour Lane, London SE5

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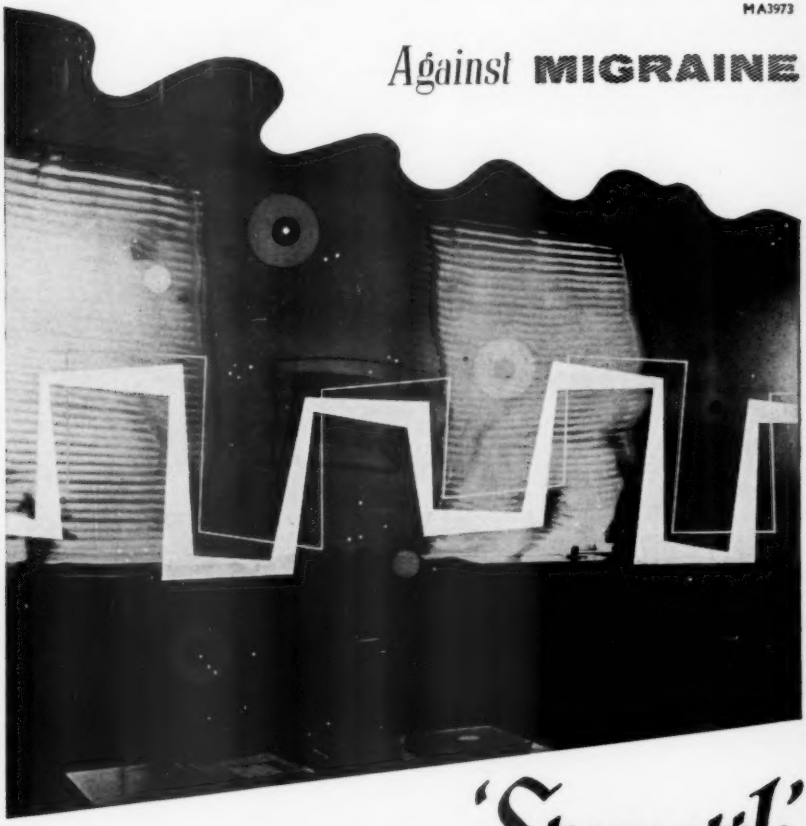
Against **MIGRAINE**



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trade mark *brand*

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'Stemetil' is a new phenothiazine derivative for the symptomatic management of migraine and kindred conditions, labyrinthine disorders, giddiness of other origins, nausea and vomiting. The drug is administered orally, or if necessary, in the form of suppositories.
Presentations: Tablets of 5 mgm. and suppositories of 25 mgm.
Detailed information is available on request.

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- Effective suppression of headache
- Complete control of nausea and vomiting
- Low toxicity in therapeutic doses

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Dramamine

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iron therapy for the arthritic

"The common association of an anaemia with rheumatoid disease has been recognised for many years . . ."

Iron?—"Blood transfusions have been given with good results but improvement has been transient".

Oral iron?—"The prolonged administration of iron by mouth has not proved very effective".

Intravenous iron?—". . . the difficulty of giving such injections to patients with joint deformity is a drawback as well as the liability to cause unpleasant side reactions".

Intramuscular iron?—"Clearly, an iron preparation for intramuscular injection free from side effects and fairly rapidly absorbed would be a great advantage . . . . It is concluded that . . . . in the treatment of the anaemia of rheumatoid arthritis . . . intramuscular iron is as beneficial as intravenous iron and easier to administer." Ann. Rheum. Dis., 1956, **15**, 51.

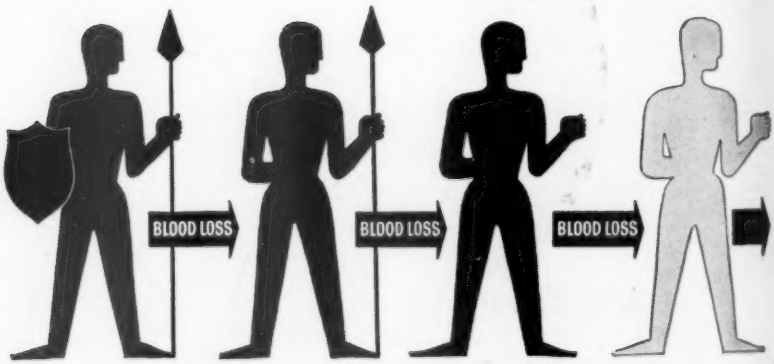
Conclusion:
A fall in haemoglobin is a common feature in arthritis and its restoration to normal is an essential part of the treatment. Restoration of a normal haemoglobin level can be quickly and surely achieved with Imferon.

Imferon TRADE MARK **IRON-DEXTRAN COMPLEX**

BENGER **Pioneers in Parenteral Iron Therapy** · **Benger Laboratories Limited, Holmes Chapel, Cheshire**

Ferrum et scutum lanceaque

(cum arte)



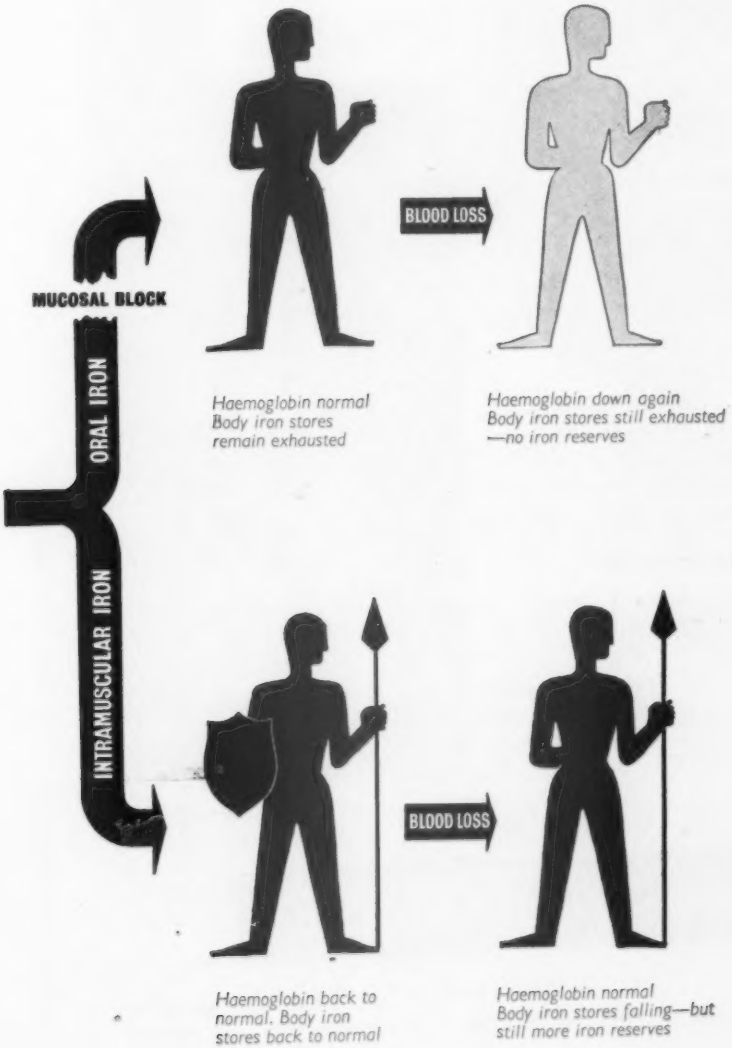
Haemoglobin normal *Body iron stores normal*	*Haemoglobin normal* *Body iron stores falling*	*Haemoglobin normal* *Body iron stores exhausted*	*Haemoglobin down* *Body iron stores still exhausted*

Suggested further reading:

Blood, 1955, **10**, 567. *Bull. N. Y. Acad. Med.*, 1954, **30**, 81.
J. Amer. med. Ass., 1956, **162**, 197. *Ann. intern. Med.*, 1955, **42**, 458.
Ann. intern. Med., 1953, **38**, 199. *J. clin. Invest.*, 1952, **31**, 543.
Brit. Encyl. Med. Pract., Med. Progr., 1956, P.47.

Imferon
Iron-Dextran Complex Trade Mark

BENGER LABORATORIES LTD., HOLMES CHAPEL, CHESHIRE · PIONEERS IN PARENTERAL IRON THERAPY


MUCOSAL BLOCK
ORAL IRON
INTRAMUSCULAR IRON
BLOOD LOSS
BLOOD LOSS
Haemoglobin normal
Body iron stores
remain exhausted
Haemoglobin down again
Body iron stores still exhausted
—no iron reserves
Haemoglobin back to
normal. Body iron
stores back to normal
Haemoglobin normal
Body iron stores falling—but
still more iron reserves

LOCAL ANAESTHESIA

INFILTRATION ANAESTHESIA demands a satisfactory spread of anaesthetic solution. It is especially valuable in the outpatient department in cases where general anaesthesia is contra-indicated.

A CLEAR CASE FOR HYALASE, the enzyme hyaluronidase.

HYALASE greatly enhances the spread and absorption of the anaesthetic. It can be easily combined with the local anaesthetic with or without adrenaline, producing a greater area of anaesthesia of satisfactory duration.

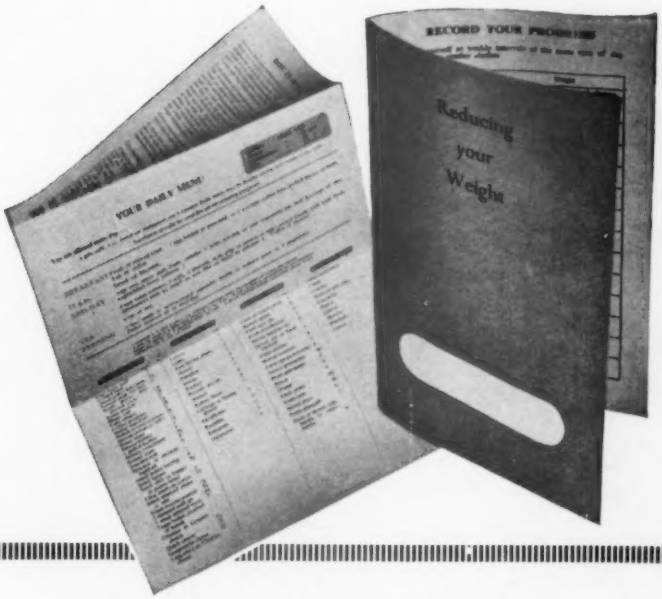
HYALASE can be successfully applied whenever infiltration anaesthesia is the method of choice.

FULLY-DESCRIPTIVE LITERATURE is available and a Technical Information Service is always at your disposal.

A clear case for **HYALASE** TRADE MARK

BENGER LABORATORIES LIMITED • HOLMES CHAPEL • CHESHIRE

A BENGER PRODUCT



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"Reducing Your Weight" is a new and easily followed guide to diet for weight reduction, and includes some simple advice and a varied menu. The folder is designed for handing to the patient, whose name may be written in a space provided on the cover.

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The Energen Dietary Service, staffed by qualified dietitians and under medical supervision, offers information and practical assistance in all dietary and nutritional problems. All services are free of charge, and practitioners are invited to apply for details.

(*Available in U.K. only*)

The Head Dietitian

ENERGEN DIETARY SERVICE

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Permit the hay fever patient
to get out and about

The hay fever patient views the summer months with dread, but his anticipation and indeed, the realisation of his pleasures and activities need not be marred. With modern therapy, the distressing symptoms can be adequately controlled.

Piriton, an improved antihistamine, is unexcelled in the degree and speed of relief that it affords and its freedom from side-effects.

Piriton is available in a wide range of practical dosage forms to suit all ages.

PIRITON

(Chlorpheniramine maleate)

Piriton Duolets in bottles of 25 and 250 Duolets; Piriton Tablets in bottles of 25 and 500 tablets; Piriton Injection in ampoules of 1 c.c. in boxes of 5 and 100 ampoules; Piriton Syrup in bottles of 4 fluid ounces.

(37 247/H

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'Sodium Amytal'

'Tuinal'

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CORK TIP IN THE RED BOX

PLAIN TIP (MEDIUM) IN THE BLUE BOX

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